Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

JUNE • 1960
Volume 10 • Number 6

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*Livingston, S., and Petersen, D.: New England J. Med. **254**:327 (Feb. 16) 1956.

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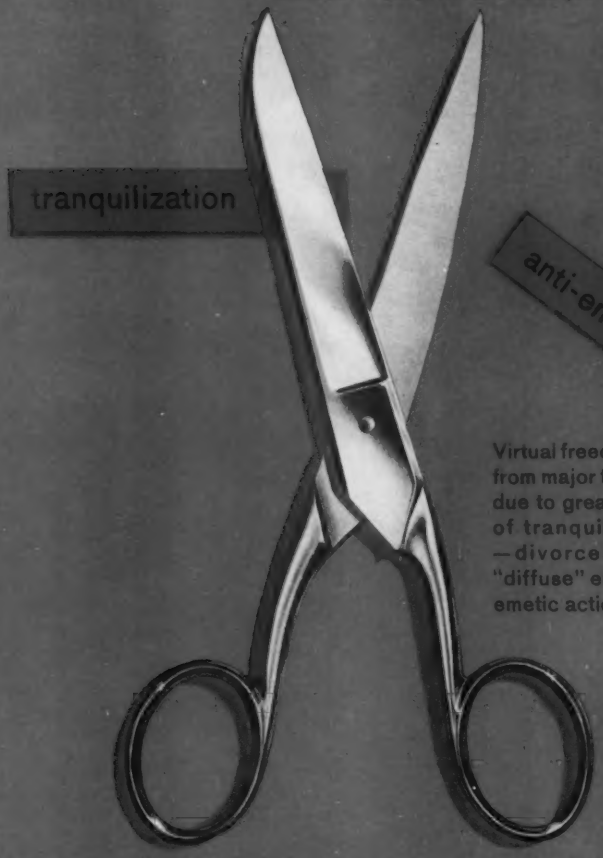

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*Kinross-Wright, J.: Newer phenothiazine drugs in treatment of nervous disorders, J.A.M.A. 170:1263, July 11, 1959.

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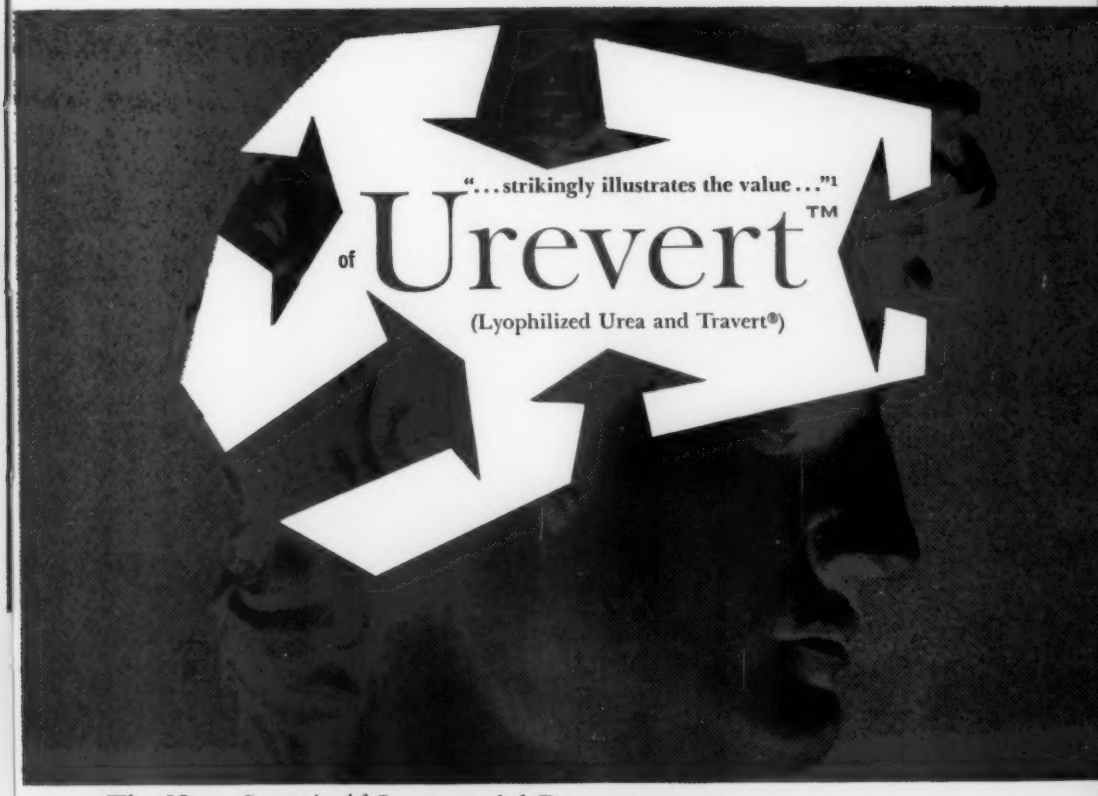

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1. Taheri, Z. E.: Urevert in Cranial Trauma and Brain Surgery, J. Internatl. College of Surgeons 32:389 (Oct.) 1959.
2. Javid, M.: Urea—New Use of an Old Agent, Reduction of Intracranial and Intraocular Pressure, The Surgical Clinics of North America, Philadelphia, W. B. Saunders Company, Aug. 1958, p. 907.

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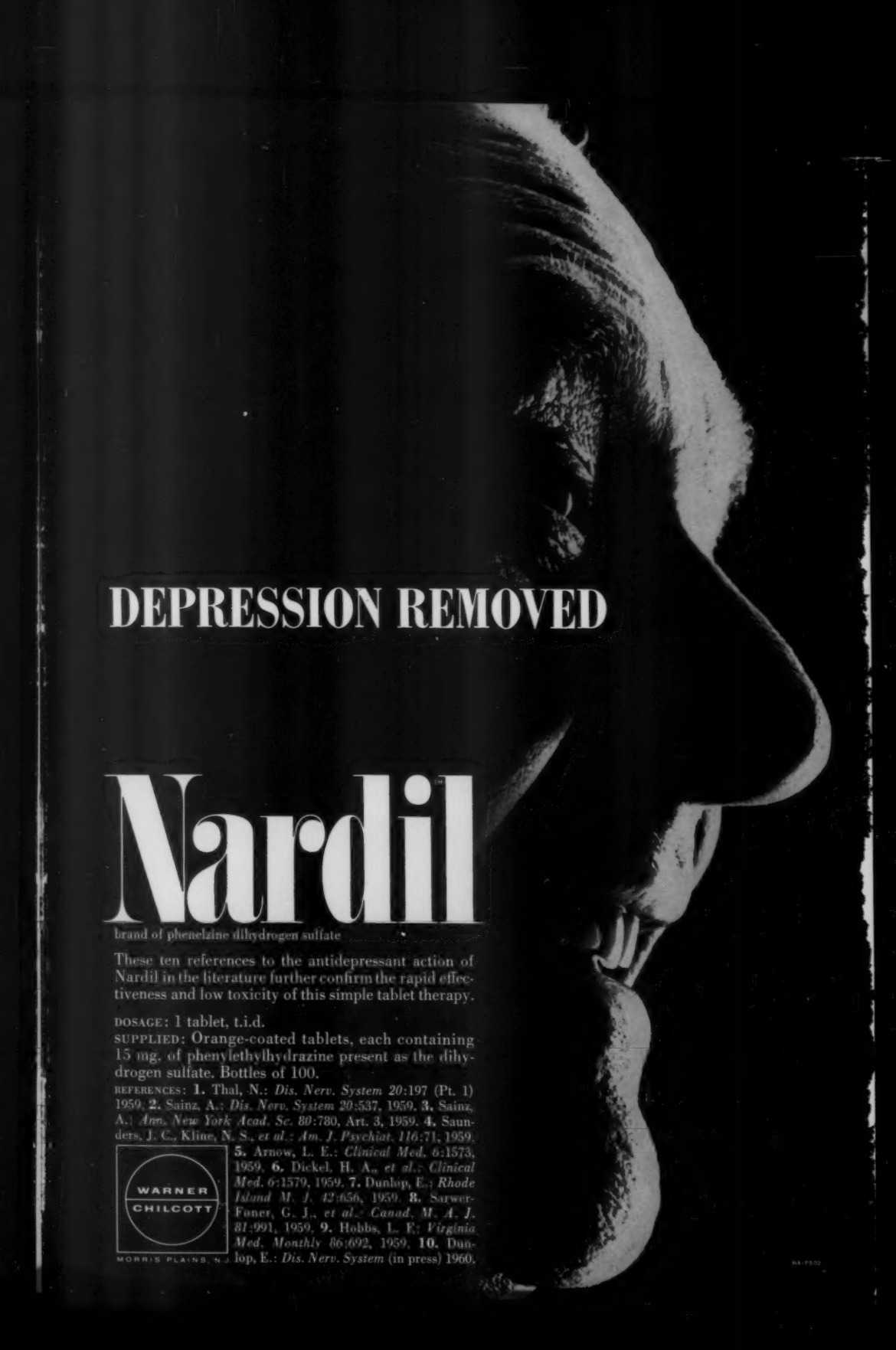

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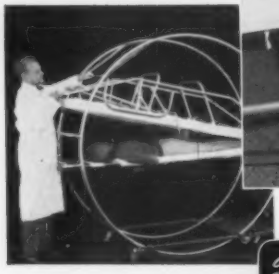

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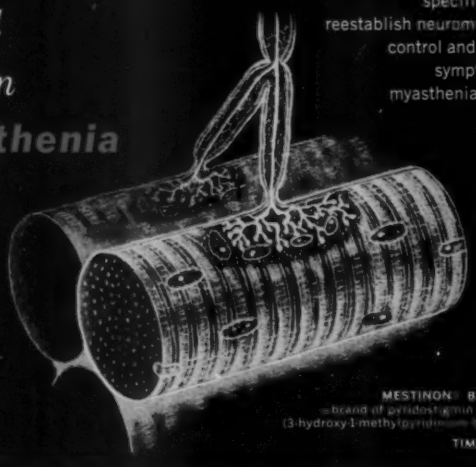

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*Doshay, L. J., and Constable, K.: Treatment of Paralysis Agitans with Chlorphenoxamine Hydrochloride, J.A.M.A. *170*:87 (May 2) 1959.

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*Ayd, F. J., Jr.: New England J. Med. *261*:172, 1959.

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1. *Wein, A.B.: Clin. Med. 6:44 (Jan.) 1959.*
2. *Vazuka, F.A.: Neurology 8:446 (June) 1958.*

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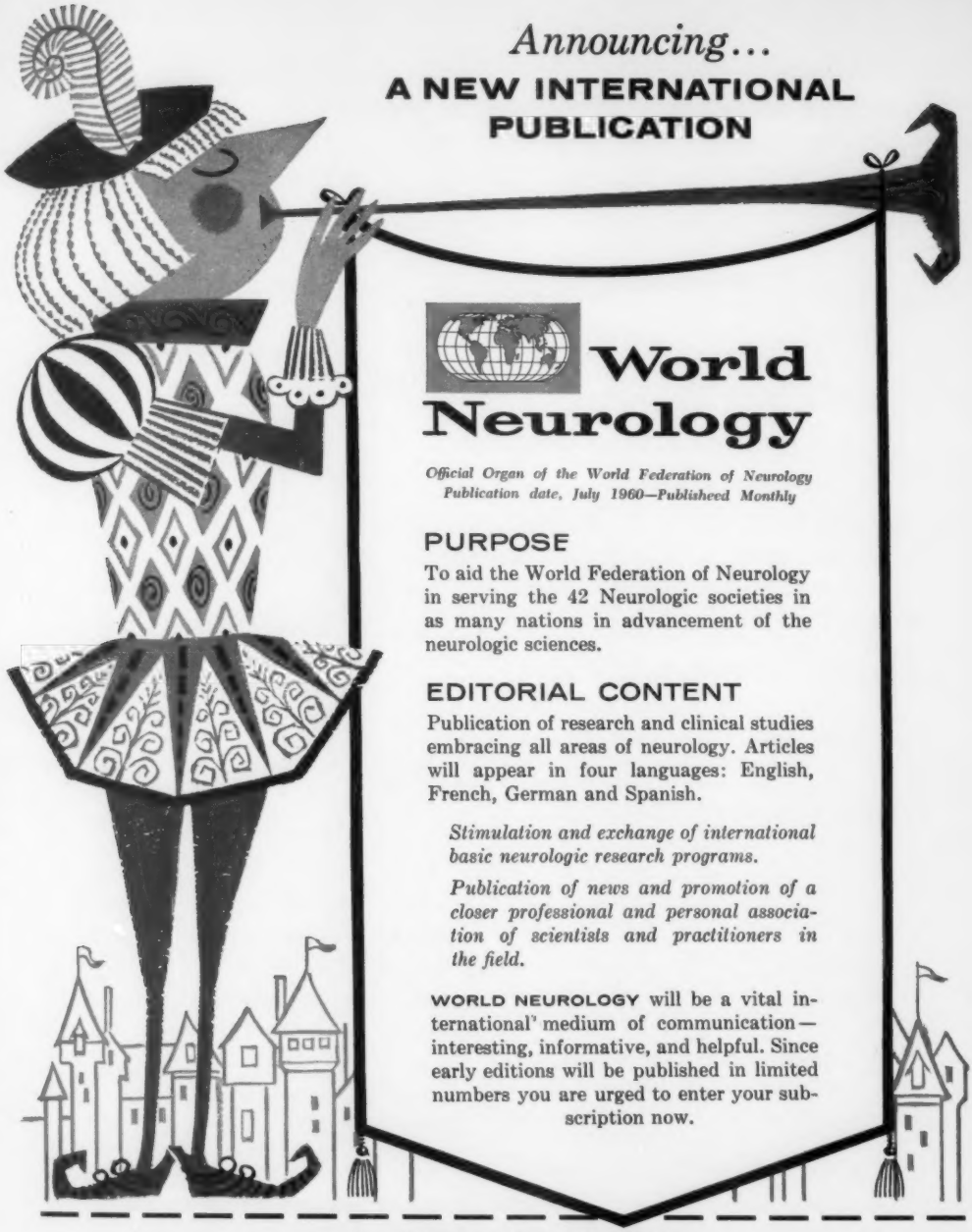

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Neurology Volume 10 • Number 6

Cerebrovascular disease

IV. A study of a Norwegian Population

A. B. Baker, M.D., S. Refsum, M.D., and E. Dahl, M.D.

THE SUBJECT of atherosclerosis is rapidly becoming one of the most important in medicine. Many theories have been proposed to account for the etiology of this condition, such as age,[1–3] mechanical trauma,[4–6] infection,[7,8] race and climate,[9,10] and nutrition.[11–13] In spite of extensive studies of all these etiologic possibilities, no definite conclusions can be drawn today as to the cause. Probably one of the greatest defects in the many studies that have been carried out is that the different investigators have failed to use uniform technics so that their observations cannot be compared. Because of this lack of uniform recording, it is impossible today to state with certainty whether atherosclerosis, particularly of the brain, differs in frequency and intensity in different areas of the world. Studies have suggested that this may be true for coronary atherosclerosis.[14] However, the failure to use similar technics makes even these observations questionable.

In order to remedy this situation, the World Federation of Neurology in 1959 established a uniform method of coding the severity of cerebral atherosclerosis. The coding system adopted was primarily a relative one in which differences in the various degrees of atherosclerosis were so clear-cut that they could be duplicated by investigators in different areas throughout the world. The coding system adopted by the World Federation of Neurology and used in these studies is as follows:[15]

- Grade 1: Opacity to a very thin plaque involving only a small part of the vessel circumference with no lumen narrowing
- Grade 2: [A] A thin plaque involving over half the vessel circumference with minimal lumen narrowing; [B] a small plaque that produces less than 25% lumen narrowing
- Grade 3: [A] A thin plaque involving the entire circumference with mild lumen narrowing; [B] a localized plaque producing 25 to 50% narrowing
- Grade 4: [A] A very thick plaque involving the entire circumference with marked lumen narrowing (pipestem); [B] a localized plaque resulting in over 50% lumen narrowing.

The present study includes 579 autopsies observed at the Ullevaal and University hospitals in Oslo, Norway. In all cases, the large arteries of the circle of Willis as well as the aorta, the internal carotids, and the coronary arteries were studied and coded, according to the system of the World Federation of Neurol-

From the Division of Neurology, University of Minnesota Medical School, Minneapolis, and the University Hospital, Oslo, Norway.

TABLE 1
GENERAL DISTRIBUTION OF ATHEROSCLEROSIS REGARDLESS OF AGE

	Grade 1	Grade 2	Grade 3	Grade 4	Total
1. Anterior communicating	52	6	2	0	60
2. Anterior basilar	172	114	24	10	320
3. Middle basilar	41	54	30	17	142
4. Lower basilar	98	94	35	22	249
5. Right anterior cerebral (anterior to anterior communicating)	66	40	7	4	117
6. Left anterior cerebral (anterior to anterior communicating)	87	34	5	3	129
7. Right anterior cerebral (posterior to anterior communicating)	44	46	2	5	97
8. Left anterior cerebral (posterior to anterior communicating)	59	43	3	1	106
9. Right internal carotid (to trifurcation)	55	125	67	18	265
10. Left internal carotid (to trifurcation)	49	110	79	12	250
11. Right internal carotid (at trifurcaiton)	72	98	36	16	220
12. Left internal carotid (at trifurcation)	96	95	49	12	252
13. Right middle cerebral (to first bifurcation)	96	145	37	28	305
14. Left middle cerebral (to first bifurcation)	99	74	46	33	252
15. Right middle cerebral (after first bifurcation)	52	50	13	6	121
16. Left middle cerebral (after first bifurcation)	42	43	8	4	97
17. Right posterior communicating	19	22	8	4	53
18. Left posterior communicating	22	15	9	0	44
19. Right posterior cerebral (first third)	114	114	30	36	294
20. Left posterior cerebral (first third)	89	107	35	30	261
21. Right posterior cerebral (after first third)	59	52	8	2	121
22. Left posterior cerebral (after first third)	59	43	8	1	111
23. Right superior cerebellar	9	6	1	0	16
24. Left superior cerebellar	6	14	2	3	25
25. Right vertebral	41	56	31	28	156
26. Left vertebral	41	73	38	21	173
27. Right posterior inferior cerebellar	22	15	9	5	51
28. Left posterior inferior cerebellar	22	22	8	6	58

ogy, as to the severity of atherosclerosis. The present report covers only our observations on the arteries of the circle of Willis. Further comparative studies of the aorta, coronaries, and internal carotids will be reported in later publications. As shown in Table 1, 28 different areas along the circle of Willis were studied and classified as to the severity of atherosclerotic changes. Each of these areas were graded from 0 to 4+ atherosclerosis. The total numerical value for the degree of atherosclerosis present in a single case was obtained by multiplying each of the 28 areas by the amount of atherosclerosis present in each and adding the total. Thus, since there were 28 areas along the circle and the greatest degree of atherosclerosis was 4+, the greatest amount of atherosclerosis possible in any case was 28 x 4 or 112. Actually, none of the cases exceeded 75 points of atherosclerosis, and most of the severe cases ranged around 30 to 50 points.

Once the total points of atherosclerosis were obtained for each case, the cases were arbitrarily divided into 4 groups: [1] no atherosclerosis; [2] mild changes, containing up to 10 points of atherosclerosis; [3] moderate changes, containing 11 to 20 points of atherosclerosis; and [4] severe changes, containing over 21 points of atherosclerosis.

Age factors. It has generally been accepted that age plays an important role in the occurrence of atherosclerosis. Some investigators feel that the aging process plays a specific role.[1,2] Others believe that age is only a coincidental process and that the older the patient, the more chance atherosclerosis has to develop regardless of the actual cause.[16] This latter view is based on the observation that atherosclerosis does appear in younger individuals and may be entirely absent in older patients.

Table 2 and Figure 1 illustrate the relationship of atherosclerosis to age in the Norwegian population studied. Atherosclerosis first appeared at the end of the third decade of life but did not become prominent until the early

TABLE 2

AGE AS RELATED TO THE INTENSITY OF CEREBRAL ATHEROSCLEROSIS

Age	None			Mild			Moderate			Severe			Total
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	
0– 5	8	7	15										15
6–10	2	1	3										3
11–15	2	2	4										4
16–20	2		2										2
21–25	2	2	4										4
26–30	1	1	2										2
31–35	3	3	6										6
36–40	6	2	8	1		1							9
41–45	5	6	11		2	2							13
46–50	5	7	12	6	2	8				1	2	3	23
51–55	10	4	14	9	2	11	2		2	1		1	28
56–60	13	11	24	11	9	20	5	1	6	4	3	7	57
61–65	11	4	15	14	6	20	11	1	12	9	12	21	68
66–70	4	10	14	20	5	25	8	11	19	10	8	18	76
71–75	4	4	8	19	9	28	7	9	16	20	15	35	87
76–80	3	3	6	12	12	24	7	13	20	13	16	29	79
81–85		1	1	5	8	13	7	8	15	22	17	39	68
86–90	1	2	3		4	4	2	7	9	3	4	7	23
91–		1	1				1	2	3	1	7	8	12
	82	81		97	59		50	52		84	84		

part of the fifth decade. No atherosclerosis was seen before the end of the third decade. Thereafter, it rapidly increased so that, by the seventh decade of life, more than 91% of patients showed some degenerative vascular changes. However, it is of importance to note that, even in the ninth decade of life, only 91% of patients revealed moderate or severe atherosclerotic changes and 9% showed none. This total absence of any degenerative changes in 9% of patients over 90 years of age certainly suggests that age alone is not the cause of this change but that increasing age merely allows this change to occur regardless of etiology.

In a previous publication,[16] a study was made of age in relation to atherosclerosis in a Minnesota population. Although this series was quite small, it might be of interest to compare the findings with the present study, particularly since the coding method was somewhat, although not exactly, similar. A comparison of these studies reveals fairly similar findings. Severe atherosclerotic lesions appeared about one-half decade earlier in the Minnesota population, beginning about age 35 years rather than 40 years as in the Norwegian population. It is interesting that in both groups at age 75 years about 65% of the cases revealed fairly extensive changes. Beyond this age, comparative studies were impossible because of insufficient cases in the Minnesota series. At the present time, the Minnesota series is being expanded so that a more accurate comparative study can be carried out.

Location of the atherosclerotic lesions. Local mechanical or hemodynamic stress has long been advocated as a possible cause of atherosclerosis. Such a theory is based chiefly upon the observation that this degenerative process

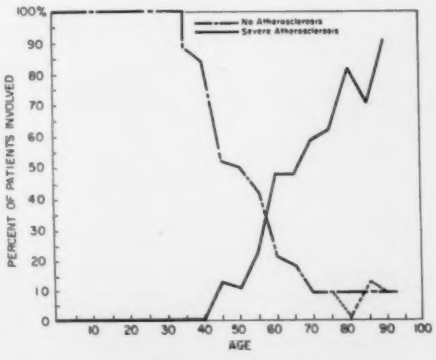

Fig. 1. Correlation of cerebral atherosclerosis with the age of the patient in the Norwegian population

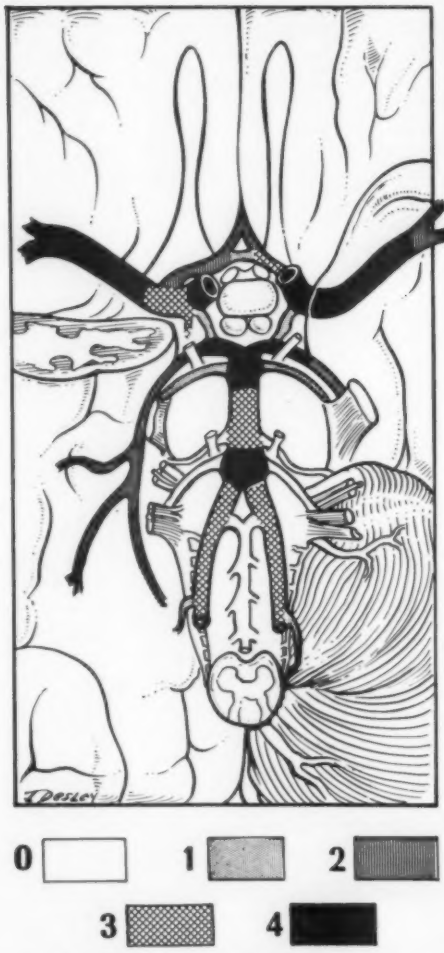

Fig. 2. Distribution of atherosclerosis of the arteries of the circle of Willis in the Norwegian population. The severity of the lesions is illustrated by the intensity of the shaded areas.

occurs most frequently at the sites of vascular fixation or bifurcation.[17] Dörfler[18] and Neubürger[19] felt that the arteriosclerotic process was more consistently related to the size of the vessels. The earliest and most severe change in their series occurred in the main stem vessels, the internal carotid and vertebrals. The large basal branches showed the following order of involvement: [1] origin of the middle cerebral from the internal carotid, [2] origin of the posterior cerebral from the basilar, and [3] the junction of the vertebrals to form the basilar. In the study of the Minnesota population, Baker and Iannone[16] observed the intensity of atherosclerotic involvement in the following order: [1] internal carotid arteries at bifurcation, [2] upper basilar artery, [3] middle and lower basilar artery, [4] middle cerebral arteries, [5] posterior cerebral artery, and [6] vertebral arteries. The degree of involvement appeared to correlate with the vessel size rather than areas of fixation or bifurcation.

In this large series of Norwegian population, the most frequently involved areas were the internal carotid arteries, both anterior to and at the trifurcation; the first part of the middle cerebral arteries; the first part of the posterior cerebral arteries; and the upper and lower parts of the basilar artery. Next in intensity and frequency of involvement were the vertebral arteries and the midportion of the basilar artery. The smaller vesesls, such as the distal portions of the middle and posterior cerebral arteries and the anterior cerebral arteries, were much less severely involved. Certain of the smaller vessels such as the communicating arteries and the cerebellar arteries were minimally implicated (Fig. 2, Table 1).

When one considers the areas of most severe atherosclerosis, it is again apparent that the lesions are not restricted to points of stress or bifurcation. This is particularly true of the lesions along the middle and posterior cerebral arteries, where long stretches of the vessels were involved. In this series, too, it would appear that the size of the vessel plays the most important role in determining the location of the atherosclerotic process. However, even this concept showed some weakness in that the middle of the basilar artery, which is one of the largest vessels, was less severely involved than both posterior cerebrals, which are of much smaller caliber.

Sex in relation to atherosclerosis. In the present study, the proportion of males to females was fairly equal, there being 313 males and 276 females. There appeared to be no

predilection of this degenerative process for the male group (Table 2). Atherosclerosis appeared at about the same time in both sexes and, with increasing age, showed a fairly uniform occurrence in both sexes. In this series, more females reached the older decades of life and, for this reason, the severe changes in the later decades appeared to predominate in women. The lack of sex influence on the cerebral atherosclerotic changes in this study agrees with the similar observation of Baker and Iannone in the Minnesota population and suggests that endocrine factors apparently play little or no role in the cerebrovascular degenerative process.

SUMMARY

1. Atherosclerotic changes of the large arteries of the circle of Willis were studied in 579 consecutive autopsies in a Norwegian population.

2. The atherosclerotic changes were graded according to the coding system published by the World Federation of Neurology. This coding system was used so that these observations might be compared with similar studies in other racial groups.

3. Atherosclerotic changes first appeared at the end of the third decade of life but did not become prominent until the early part of the fifth decade; 9% of individuals over 90 years of age had no changes.

4. The most frequently involved areas were the internal carotid arteries, the first part of the middle cerebral arteries, the first part of the posterior cerebral arteries, and the upper and lower parts of the basilar arteries.

5. Sex seemed to play little role in the frequency or intensity of this process.

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Brain radiation in newborn rats and differential effects of increased age

I. Clinical observations

J. N. Yamazaki, M.D., L. R. Bennett, M.D.,
R. A. McFall, M.D., and C. D. Clemente, Ph.D.

THE DIFFERENTIAL response to irradiation with respect to age is strikingly demonstrated when one compares the effects of ionizing rays on fetal and adult mammalian nervous system. During the earliest stage of gestation in the rat, the preimplantation stage, irradiation results in high prenatal death, although the survivors show very little gross abnormalities in the nervous system.[1,2] It has been well established that, during the remainder of gestation, the fetal nervous system in the rat is very sensitive to irradiation.[3–7] Various malformations that have been produced include hydrocephalus, microcephalus, anencephaly, meningocele, and encephalocele. The studies of Job,[4] Warkany and Shraffenberger,[5] and others established the relative sensitivity of the fetal nervous system at precise stages of development and the effect of varying doses of irradiation. Hicks[2,7] stressed the importance of neuroblasts as radiosensitive cells, damage to which results in abnormal development of the fetal rat brain. In contrast to the newborn brain, the adult brain has been considered to be relatively radioresistant but is by no means insensitive to large doses of radiation, as demonstrated by Clemente,[8,9] Arnold,[10] and Davidoff.[11]

Not long after the discovery of x-rays by Roentgen in 1895 and the discovery of radium by the Curies in 1898, reports appeared noting the relative radiosensitivity of the brain of young animals as compared to adults.[12,13] Although some of the early work is difficult to correlate with present standards of dosage measurements, later studies generally verified the earlier findings.[14–16] Retardation in body size and brain size has also been noted as a result of irradiation. Neurologic findings such as ataxia, paralysis, seizures, blindness, deafness, and retarded mental performances were also noted. However, a systematic study, varying the dose with increasing age during the neonatal period and observing the acute and long-term effects of the irradiation to the head, has not been reported to our knowledge. Such an approach has yielded much valuable information in embryonic studies, since some interest has been focused on how irradiation interferes with normal growth and development.

Consideration of some of the phenomena associated with the growth of the brain during the neonatal period suggests the possibility of a changing pattern of response to irradiation with increasing age. A wealth of information is available concerning the developmental biochemical changes during the newborn period.[17,18] Inasmuch as the rat was used in this investigation, reference will be made mainly to the related anatomic, functional, and biochemical changes observed in this animal. Our study was undertaken to observe systematically the acute and long-term effects of a single direct radiation dose to the brain of neonatal and young rats.

METHODS

A total of 112 Wistar and Long-Evans rats, ranging in age from 8 hours to 15 days, received radiation to the head. The animals

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TABLE 1

SUMMARY OF EFFECTS OF RADIATION TO THE HEAD OF NEWBORN RATS

Age of animals	*Radiation dosage*	*Number of animals radiated*	*Numbers of animals in which neurologic signs existed**	*Numbers of animals in which other signs existed***
8 hours	125 r	3	0	2
1 day	300 r	3	2	0
1 day	500 r	8	7	4
1 day	1,000 r	5	3	4
2 days	500 r	5	4	1
2 days	1,000 r	6	6	4
4 days	300 r	6	4	1
5 days	500 r	15	6	6
5 days	1,000 r	1	1	1
6 days	500 r	2	0	0
6 days	1,000 r	1	0	0
7 days	300 r	2	0	0
8 days	500 r	6	0	0
8 days	1,000 r	5	4	4
9 days	500 r	5	1	1
14 days	500 r	2	1	1
14 days	1,000 r	4	0	3
15 days	500 r	2	0	0
15 days	1,000 r	5	0	0

* Tremor, uncoordinated gait, inability to right themselves, leg dragging, chronically abducted limbs, lunging movements, head deviation, elevated pelvic posture

**Microencephaly, small eyes, cataracts

were irradiated utilizing the following physical factors: 120 kv. Picker Therapy Unit focal skin distance, 20 cm., 5 milliamperes, 1mm. aluminum added filtration, half value layer 1.95 mm. aluminum, output 93 r per minute (calibrated with Victoreen thimble chamber and unit density phantom), field size 1.2 cm. diameter cone.

Each animal was placed on a frame, and only its head was exposed to the beam. The younger animals were held in place with gummed tape. The older ones received Myotal intraperitoneally to quiet them for the procedure. Single doses of radiation were given at 4 levels: 125, 300, 500, and 1,000 r. Observations were also made on 48 control animals.

In order to maintain uniform conditions in the early neonatal period, all of the animals in a litter, whether they were to be irradiated or not, were removed from their mother during the time of exposure. Forty-eight hours after irradiation, 28 animals were autopsied. The remaining 84 rats were observed for clinical evidence of irradiation damage to the nervous system. Motion pictures were taken of some rats, showing neurologic involvement. The longest period of observation was fourteen months; however, animals that appeared moribund were sacrificed. Other adult animals with severe nervous system involvement were sacrificed at varying intervals even if they were not moribund. At autopsy, animals were perfused through the heart with 10% formalin after preliminary perfusion with normal saline solution. The entire brain and sections of the viscera were removed and saved for microscopic study. Radiograms of some of the adult animals were taken, and the skull area was determined by tracing the outer table of the cranium on roentgen film with a planimeter.

OBSERVATIONS

A summary of the observations of the irradiated animals is shown in Table 1. It will be noted that, with the radiation doses used in this study, the development of signs involving the nervous system is closely associated with the younger newborns, particularly those ra-

TABLE 2

WEIGHT OF IRRADIATED RATS AT 3 MONTHS OF AGE

Radiation dose	*Age at irradiation*	*Number of animals*	*Weight in grams, range*	*Average weight in grams*
		MALE RATS		
Controls		20	180–310	259
500 r	1– 5 days	10	170–280	234
	6–15 days	5	255–290	269
1,000 r	1– 5 days	2	140–220	180
	6–15 days	4	220–260	246
		FEMALE RATS		
Controls		17	160–225	185
500 r	1– 5 days	12	125–185	165
	6–15 days	12	170–220	198
1,000 r	1– 5 days	2	110–140	125
	6–15 days	6	140–190	175

TABLE 3

MORTALITY UNDER 3 MONTHS OF AGE IN HEAD-IRRADIATED NEWBORN RATS WITH RESPECT TO AGE AND DOSE

Radiation dose	*Age at the time of irradiation*		
	Under 4 days	*5–6 days*	*7–15 days*
125 r	0 [deaths] (3) [animals radiated]		
300 r	3 (9)		0 (2)
500 r	5 (13)*	5 (17)	0 (3)
1,000 r	9 (11)	1 (2)	2 (14)

*1 anesthetic death

Figures in parentheses indicate total number irradiated in each group.

TABLE 4

DEVELOPMENT OF PATHOLOGIC NERVOUS SYSTEM SIGNS IN HEAD-IRRADIATED RATS WITH RESPECT TO AGE AND DOSE

Radiation dose	*Age in days of rats when irradiated*								
	1	*2*	*4*	*5*	*6*	*7*	*8*	*9*	*14–15*
125 r	0 (3)								
300 r	2 (3)		4 (6)			0 (2)			
500 r	6 (8)	5 (5)		7 (15)	0 (2)		0 (6)	0 (3)	1 (4)
1,000 r	5 (5)	6 (6)		1 (1)	0 (1)		4 (5)		0 (9)

Figures in parentheses indicate total number irradiated in each group.

diated under 5 days of age. In addition, there were deleterious effects on the general health and growth of 1- and 2-day-old animals receiving 500 or 1,000 r. Rats radiated under 4 days of age tend to show retarded growth (Table 2).

Of the 84 irradiated animals, 27 died. The highest mortality was found in the animals irradiated in the immediate newborn period. With one exception, all deaths under 3 months of age occurred in rats that received radiation within the first four days of life. Of the 36 animals irradiated under 4 days of age, 17 died within three months after irradiation; however, 3 of the deaths were attributed to anesthesia. Of the 1,000-r animals, 7/11 animals succumbed during the first three months, 4/13 of the 500-r animals, 3/9 of the 300-r animals, and none of the 125-r animals. The average survival periods of the animals that died under 3 months of age were 0.9 months for the 1,000-r rats and 2.3 and 2.4 months for the 300- and 500-r animals, respectively. Even in the older animals, the proportion of deaths was greater in the animals receiving a higher dose of radiation, as shown in Table 3.

Neurologic signs were present in 18 (67%) of the animals that succumbed. Of the 38 control animals, 8 died, 1 from anesthesia. Signs involving the nervous system developed in 41 of the 84 irradiated rats. It will be noted in Table 4 that nearly 69% of the rats under 5 days of age showed neurologic involvement in contrast to 15% irradiated after 5 days.

Of the 9 animals receiving 500 r after 5 days of age, only 1 had signs involving the nervous system as compared to 18 of the 28 500-r animals under 5 days of age. The difference in extent of involvement of the nervous system in the 2 groups is illustrated by the following examples. Animal No. 32 received 500 r when 5 days of age. Tremors became progressively severe from the age of 1½ months. Incoordination developed. Weakness of the hind limbs was noted from the third month. Rat No. 18, which received 500 r fourteen days after birth, was first noted to have tremors at 10 months.

Animals radiated with 1,000 r on the first day of life reveal a distinctly different picture. Typical of this group are RL 72, 73, and 77. By the second week of life, they could easily be separated from their control litter mates by their small size, weighing an average of 18 gm. compared to 39 gm. for the controls. Marked tremor was already present. Eyes were narrowed and small. They had a tendency to drag their hind limbs and difficulty in righting themselves. One of the animals revealed marked hyperactivity, running and darting about the cage in a random manner. At autopsy, the scalp of another rat in this group, RL 56, was very thin, with very little subcutaneous tissue. The meninges appeared fibrous, and the dura was firmly adherent to the brain surface, although it was possible to separate it from the cerebral cortex. The posterior part of the cortex was depressed, as if the cortex was thin in this area.

Tremor of the entire body was the most frequently observed neurologic sign and developed in 36 rats. Animals irradiated under 5 days of age tended to show tremors within the first few months of life. Those receiving 1,000 r in the early neonatal period were noted to have marked tremors even by the second week of life. Abnormal gait in one form or another was present in 24 animals. Some were noted to have incoordination of the extremities associated with jerky, irregular steps. A few rats dragged their legs with an inability to support their body weight, although movement of the extremities was present when the animals were held off the floor. A propulsive type of gait was noted in 2 animals. Elevation of the rump when walking was noted especially in some of the 500-r animals that were irradiated early but had no other severe neurologic signs. Small heads were noted in 23 animals (Table 5). These animals were considered to have small heads only after several independent concurring observations were made. Of these small-headed animals, 5 were noted to have small eyes.

Cataracts developed in 7 rats, bilaterally in 2. In 5 of these, small eyes were observed before onset of cataract. On the other hand, 4 other rats with small eyes did not have cataracts. Of the 7 rats with cataracts,6 had small heads. The 1 rat that was not considered to have a small head was a female weighing 140 gm. at 3 months of age, compared to the average weight of 185 gm. for the control female rats at 3 months. The earliest observation of

TABLE 5

INCIDENCE OF SMALL HEADS IN HEAD-IRRADIATED NEWBORN RATS

Radiation dose	*Age in days of rats when irradiated*									
	1	*2*	*4*	*5*	*6*	*7*	*8*	*9*	*14*	*15*
125 r	2* (3)									
300 r	0 (3)		1 (6)			0 (2)				
500 r	1 (8)	1 (4)		5 (8)	0 (7)	0 (3)	0 (6)	0 (3)	1 (2)	0 (2)
1,000 r	4 (5)	4 (6)		0 (1)			4 (5)		3 (4)	0 (5)

* 8 hours

Figures in parentheses indicate total number irradiated in each group.

a cataract was in rat C9, which received 300 r on the fourth day. A cataract was noted in the sixth week in one eye and by the sixth month in the opposite eye. The eyes were small, sunken, and almost closed by the sixth month. Interestingly enough, the rat that had a cataract at 8½ months received 1,000 r on the fifth day of life. The greatest incidence of cataracts occurred in animals radiated on the fifth day and receiving 500 r. Of the 15 rats receiving 500 r, 4 had cataracts. It is possible that a higher incidence of eye pathology might have been found in the animals radiated under 4 days of age had they been able to survive. The neuropathologic findings were very closely correlated with observations on behavior and are being published separately.

DISCUSSION

In this study, we wished to stress the differential radiosensitivity of the neonatal rat brain from birth through the fifteenth day. With head radiation doses of 125, 300, 500, and 1,000 r, the most severe brain reactions were found in rats radiated on the first three to four days postnatally. Animals irradiated on the fifth postnatal day definitely showed fewer neurologic signs than rats radiated on the first four days. Administration of 500 r to the head of the 5-day-old rat produced neurologic signs in little less than half of the irradiated rats, whereas all of the animals irradiated with 300 and 500 r before this time showed some evidence of central nervous system involvement and 1,000 r often proved lethal in the first few days of life. After the fifth day, there was a marked decrease in the incidence and severity of the neurologic signs, and radiation on the fifteenth day resulted in no visible neurologic findings, even though the animals were often radiated with 1,000 r. In many rats radiated at the age of 3 months and over with 1,000 r, no clinical neurologic findings have been noted.[19]

A dose as low as 40 r administered to the rat fetus on the ninth day of gestation can cause cerebral malformations.[6] Doses of 100 and 200 r administered during the remainder of the gestational period result in a variety of malformations such as exancephaly, encephaloceles, microencephaly, and hydrocephalus.[2,4,5,7] During the preimplantation stage in the rat (that is, the first through the eighth day of gestation), a dose of 200 to 400 r will result in a high percentage of prenatal deaths but a very low incidence of brain malformations in the survivors.[1] Hence, in a period of two or three days, a tenfold increase in radiosensitivity in the developing nervous system occurs. This has been associated with the rapid appearance of an abundance of neuroblasts in the developing brain. For a comprehensive review of these studies, one can read the article by Rugh.[20]

The neurologic findings observed in the rats in this study are similar to the findings of other investigators in their studies on irradiated newborn and young guinea pigs, rabbits, kittens, and dogs.[12–15,21,22] Tremors, clonic twitching, epileptoid seizure, paralysis of extremities, retardation of head and body size, and poor mental performance have been noted. Pre-

viously, however, a sequential age-dose relationship during the neonatal period had not been demonstrated.

The effect of radiation on the developing human brain is not as well documented as are the animal studies. Murphy[23,24] has reported the occurrence of microencephaly, mental defects, hydrocephaly, ossification defects of the cranial bones, eye defects, and skeletal abnormalities in children born after maternal pelvic irradiation. Intrauterine exposure of the fetus to atomic radiation in sufficient amount to cause acute radiation effects on the mother has resulted in children with head circumferences significantly smaller than in the control group.[25,26] Information concerning irradiation of the head alone in infants and children is scanty. Children irradiated for scalp lesions showed epilation in three weeks. After a year or so, hemiparesis and seizures developed,[27,28] and a subdural hematoma was reported in 1 patient. In contrast to this, over 3,000 persons—many of whom were children—who received epilating doses of radiation for treatment of tinea capitis were noted to have no evidence of injury to the brain.[29] In another report, children over 3 years of age who received radiation to the head for a similar condition did not show any abnormal neurologic findings;[30] however, to avoid any possibility of injury, children under 3 years were not radiated. Periods of somnolence lasting four to fourteen days were noted in 30 out of 1,100 children epilated by radiation therapy for ringworm of the scalp.[31] A similar type of reaction was noted in adult human volunteers who received approximately 150 r to the diencephalic area.[32] Disturbance of sleep-wake patterns and changes in gonadal function also were noted. In this regard, radiosensitivity of the hypothalamus and brain stem has been demonstrated in recent studies by Clemente and Holst[9] and Arnold, Bailey, and Harvey.[33]

There is a paucity of information concerning the effect of therapeutic radiation for brain tumors in infants and children. However, a careful study of such cases from the standpoint of the age-dose effect may help to clarify the degree of radiosensitivity of the brain at various age levels in infants and children in order to define the limits of permissible therapeutic doses. A report on the survivors of the atomic bomb explosion who exhibited no signs of burns, trauma, or generalized radiation illness, but who were assumed to have been radiated to the head alone, reveals that the most extensive involvements of the brain were in children.[34]

The adult human brain can withstand relatively large doses of initial irradiation; however, delayed reaction may develop one to four years later. With doses considered therapeutic for localized skin neoplasm, radiation has resulted in damage to the brain. With a dose of 2,500 r, localizing neurologic signs developed two years after the irradiation. Brain necrosis secondary to obliterative vascular lesions was found.[35] Intense proliferation and hypertrophy of the astroglia, which then degenerated into an amyloid-like substance, occurred in a person four years after the last in a series of 2 exposures twenty-two months apart which totaled 9,600 r.[36]

There is some evidence that the cerebral vessels react differently than the extracerebral vessels to radiation. When the heads of rabbits were irradiated, it was noted that intimal proliferation, fibrinoid degeneration, and occlusion developed in the cerebral vessels, whereas no such reaction occurred in the meningeal vessels and in some of the superficial cortical vessels.[37] It has been demonstrated that vasoconstriction and vascular occlusion develop in the retinal vessels of newborn kittens exposed to high concentrations of oxygen,[38] but whether other cerebral vessels react similarly has not been shown. This is of particular interest as oxygen enhances the ionizing reaction, whereas the anoxic and hypoxemic state reduces the radiation sensitivity.

A temporal correlation can be made between the radiosensitivity of the neonatal brain during the first week of postnatal life and the anatomic and chemical changes that occur during this period. During the first postnatal week, the cell density of the brain is still quite high;[39,40] rapid vascular proliferation is taking place.[41] Differentiation of the neurons is far from complete, and glial cells still seem to increase in number.[42] The newborn is still able to survive anoxic conditions relatively well. At the same time that the brain develops a relative radioresistance, the chemical composition of the brain changes. There is a marked

increase in the accumulation of the brain components, particularly of proteins and lipids.[43] Desoxyribonucleic acid (DNA) content is still increasing. A fourfold increase in DNA occurs between the second and sixteenth postnatal day, after which further increase is hardly noticeable.[44] Oxygen uptake, which changes very little during the first week of life, increases twofold in the following three weeks.[45,46] There is an increase in respiratory and related enzyme activity.[47] It is interesting that the rat brain is relatively radioresistant while these dynamic biochemical changes are occurring after the first postnatal week and that the period preceding the changes is the more radiosensitive one.

SUMMARY

A total of 112 rats ranging in age from 8 hours to 15 days received single doses of radiation directly to the head at the following levels: 125, 300, 500, or 1,000 r.

Forty-eight hours after irradiation, 28 animals were autopsied. They showed no clinical evidence of damage to the nervous system and could not be distinguished from the controls.

The remaining 84 animals were observed for periods of up to fourteen months after irradiation. During the first week of life, the mortality rate, amount of growth retardation, and incidence and severity of neurologic findings were greatest in animals irradiated during the first few days and increased with the dosage. A certain tolerance to irradiation developed by the end of the first postnatal week.

1] The highest mortality was found in animals irradiated in the immediate newborn period. All spontaneous deaths under 3 months of age occurred in rats that received radiation within the first four days of life.

2] Nearly 70% of the rats radiated under 5 days of age had neurologic findings, as compared to 15% of those radiated after 5 days. The most common neurologic findings were tremors, incoordination, leg dragging, inability to right themselves, and small head size.

3] The adult body weight of the animals radiated during the first five days of life was lower than that of animals radiated after the fifth day, and this was best demonstrated in the 1,000-r group. Animals radiated during the first two days of life often weighed only half as much as their controls.

4] Cataracts developed in 7 rats, of which 6 were noted to have small heads. Cataract incidence was greatest in animals irradiated with 500 r on the fifth day. The low incidence of cataracts in the animals irradiated under 5 days of age may have been due to the great number of early deaths in this group, before cataracts could develop.

5] Small heads were observed in 23 animals.

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A complete list of references will be given in the July issue at the end of Part II.

Effect of acetazoleamide (Diamox) on encephalopathy induced by water excess and hypernatremia

August G. Swanson, M.D.

ABNORMALITIES of function of the central nervous system are the earliest and most prominent symptoms of rapid changes in the osmolality of body fluids.[1] Acute overhydration (hypoosmolality) produces agitated delirium, convulsions, and coma.[2] Water depletion (hyperosmolality) produces confusion, lethargy, and coma.[3] Heretofore, treatment of the encephalopathy caused by acute fluid and electrolyte imbalance has been limited to the correction of abnormal electrolyte concentrations by administration of appropriate amounts of salt and water. Such therapy fails to arrest the central nervous system symptoms quickly; indeed, treatment of hyperosmolality with glucose water or hypotonic salt solutions may precipitate convulsions.[3]

Woodbury,[4] studying rats, has shown that, when a water load is given, the intracellular sodium concentration in the brain rises and the electroshock seizure threshold is lowered. Acetazoleamide lowers the intracellular sodium and increases the electroshock seizure threshold.[5] This action of acetazoleamide on brain sodium suggested that it might be a useful drug in treating the encephalopathy produced by salt and water imbalance. The studies herein reported demonstrate the effect in cat and man of acetazoleamide on the electroencephalographic abnormalities induced by alterations in salt and water balance.

MATERIALS AND METHOD

Young cats weighing between 1.1 and 1.7 kg. were anesthetized with ether. A tracheostomy tube, arterial and venous cannulae, and phonograph-needle skull electrodes were installed. In 1 group of animals, a wettable cellophane bag attached to a plastic tube was inserted into the peritoneal cavity through a small midline ventral incision. All animals were paralyzed with 3 mg. of d-tubocurarine and artificially breathed with a Palmer pump. Anesthesia was discontinued, and two to three hours were allowed for recovery. Alveolar pCO_2 was monitored with a Liston-Becker infrared CO_2 analyzer through a catheter inserted into the tracheostomy tube. Ventilation was adjusted so that the arterial *p*H (measured at 37° C. with a Cambridge Model R *p*H meter equipped with a Coleman microchamber glass electrode) ranged between 7.38 and 7.44. The electroencephalogram was recorded using bipolar linkages between frontal, central, and occipital electrodes on each side of the skull. In selected animals, intraarterial blood pressure was recorded with an electronic pressure transducer recording through a Sanborn oscillograph. Serum sodium concentration was used as an index of the osmolality of the extracellular fluid. Sodium concentration was measured with a Baird flame photometer on serum obtained from centrifuged 3-cc. clotted arterial blood samples.

A patient with overhydration encephalopathy was given acetazoleamide intravenously while the electroencephalogram was recorded using standard clinical technics.

RESULTS

The injection of 50 mg. (1 cc.) of acetazoleamide intravenously in kittens consistently

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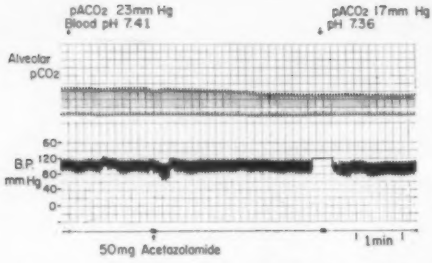

Fig. 1. Simultaneous recording of alveolar pCO_2 and blood pressure illustrating the fall in the partial pressure of carbon dioxide after injection of acetazoleamide. Arterial blood *p*H decreased as alveolar carbon dioxide fell, suggesting an increased H_2CO_3 concentration in blood.

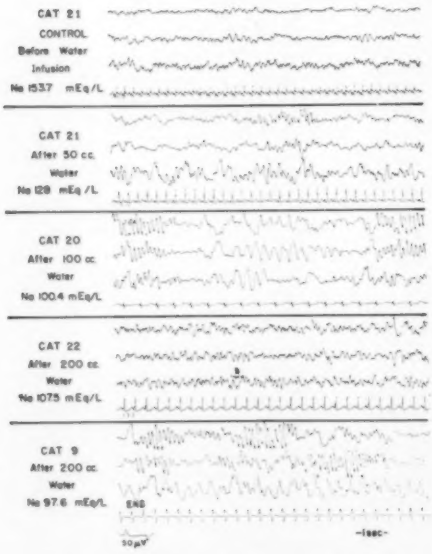

Fig. 2. Variability of electroencephalographic changes with a water load in 4 animals

produced a fall in the alveolar pCO_2 and a drop in the arterial blood *p*H (Fig. 1). Blood pressure and heart rate were unaffected by the drug. The electroencephalogram was not modified by acetazoleamide unless abnormalities had been induced previously by the creation of water and electrolyte imbalance or by hyperventilation.

Effect of acetazoleamide in acute overhydration. Acute overhydration was induced in 8 cats by the intravenous infusion of 5 or 2½% glucose in water at a rate of 5 cc. per minute. The serum sodium was reduced from 152.8 ± 8 mEq. per liter to a range of 110.7 ± 10 mEq. per liter by the first 100 cc. of water. Serum sodium values as low as 70 mEq. per liter were reached when 500 cc. of water was given. In 4 animals, the electroencephalogram showed progressive changes consisting of slower frequencies and increased amplitude. Sharp waves appeared intermittently. The abnormalities induced in the electroencephalogram by overhydration varied, and some animals required larger quantities of water to produce comparable electroencephalographic changes (Fig. 2). When the infusion was stopped, the electroencephalogram became less abnormal over a period of time varying from fifteen minutes to one hour. This tendency to return toward a normal electroencephalographic pattern was less if larger quantities of water were given.

When clear-cut and persistent abnormalities in the electroencephalogram were present, 50 mg. of acetazoleamide was injected intravenously. A striking improvement in the tracing followed the injection (Fig. 3). Within one and one-half to fourteen minutes, the cortical rhythms showed a drop in amplitude and an increase in frequency. The over-all electroencephalographic pattern approached the appearance of the control tracings. The infusion of more water after acetazoleamide had been given caused only minor and transient slowing of the electroencephalogram, even though serum sodium concentrations fell as low as 70 mEq. per liter.

Significant electroencephalographic alterations were not seen in 3 animals, even though the serum sodium concentrations fell to a range of 97 ± 3 mEq. per liter. Acetazoleamide had no effect on the unchanged electroencephalographic patterns in these animals.

Acetazoleamide was given to 1 animal before the infusion of glucose water was begun. The electroencephalogram remained constant throughout most of the experiment, and, when the serum sodium concentration was 79.3 mEq. per liter, only occasional bursts of high voltage sharp activity appeared against a background

rhythm that was similar to the control tracing.

Effect of acetazoleamide in acute hypernatremia. Hypernatremia was induced in 8 animals. In 2, 30 to 40 cc. of 1 normal sodium chloride was injected directly into the peritoneal cavity. In 6 animals, the serum sodium was raised by dialysis through a wettable cellophane bag lying in the peritoneal cavity. Using either technic, serum sodium concentrations rose from a range of 155 ± 8 to 190 ± 16 mEq. per liter.

High voltage slow electroencephalographic patterns with intermittent bursts of sharp waves developed in 6 animals; 4 of these were then given 5% glucose in water intravenously, which lowered the serum sodium concentration to a level of 136 ± 4 mEq. per liter. The electroencephalograms became more abnormal when water was given, and high voltage sharp waves were more prominent. Intravenous acetazoleamide, 50 mg., caused prompt lessening of the high voltage sharp activity and return of the electroencephalographic pattern toward normal in 3 animals (Fig. 4); 1 animal showed no change in the electroencephalogram when acetazoleamide was given.

Before glucose water was administered, 2 animals with hypernatremia were given 50 mg. of acetazoleamide. In both animals, there was a prompt improvement in the electroencephalogram (Fig. 5). Acetazoleamide was administered before induction of hypernatremia in 1 animal, and, although the serum sodium was raised to 190 mEq. per liter and fell to 100.6 mEq. per liter with hydration, the electroencephalogram remained essentially unchanged throughout the experiment.

Significant changes in the electroencephalogram did not develop in 1 animal with a serum sodium of 185.6 mEq. per liter, and hydration did not produce abnormalities.

Effect of acetazoleamide on overhydration encephalopathy in a human being. A 42-year-old woman with metastatic carcinoma of the breast underwent pituitary stalk section. The operative approach was through a right frontal flap. Preoperative endocrinologic, neurologic, and renal investigations demonstrated no abnormalities. She tolerated the procedure well. During the first week after surgery, she was alert and recovering satisfactorily.

Initially, she had a high oral fluid intake

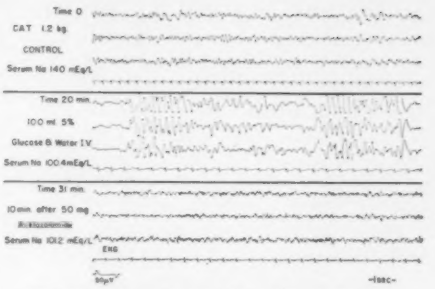

Fig. 3. Effect of acetazoleamide on the electroencephalogram in overhydration

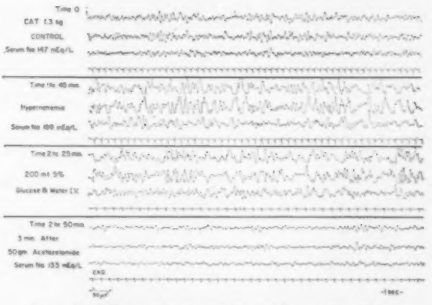

Fig. 4. Effect of acetazoleamide on the electroencephalogram in overhydration superimposed on hypernatremia

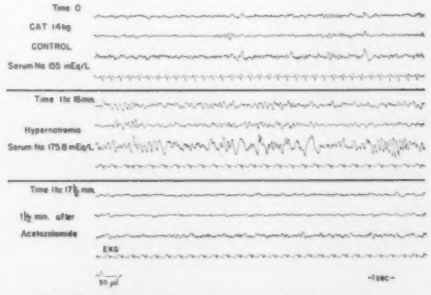

Fig. 5. Effect of acetazoleamide on the electroencephalogram in hypernatremia

and a moderate diuresis. On the fourth postoperative day, she entered the oliguric interphase that occurs after pituitary stalk section.[6] On the sixth postoperative day, she had several bouts of vomiting and demonstrated unsustained nystagmus on lateral and upward

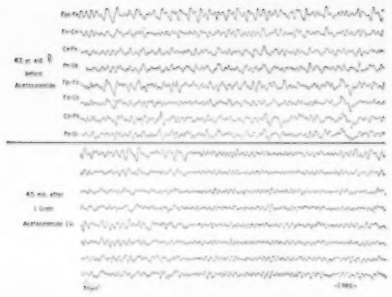

Fig. 6. Effect of acetazoleamide on the electroencephalogram in overhydration encephalopathy in a human being

gaze, hyperactive gag reflex, fine tremors of the right hand and foot, hyperactive deep tendon reflexes, and left extensor plantar response. Vomiting continued intermittently, and, on the eighth postoperative day, a serum sodium of 125 mEq. per liter was reported. Meanwhile, she had received 3,000 cc. of 5% dextrose and water intravenously that day. Early on the ninth postoperative day, she had convulsive movements of the left leg without loss of consciousness. Neurologic examination demonstrated orientation to place and person but inability to fix the time more closely than the year. She had a brief attention span and could not do arithmetic problems. Quick, twitching movements of the mouth and extremities were noted, and, on extension of both arms and legs, a flapping tremor, indistinguishable from the tremor of hepatic encephalopathy, was seen. The deep tendon reflexes were hyperactive, and the jaw jerk was abnormally brisk. Snouting and sucking responses, bilateral extensor plantar responses, sustained ankle clonus, and unsustained patellar clonus were elicited. The serum sodium concentration had fallen to 105 mEq. per liter.

The patient was given 1 liter of isotonic saline but was unchanged clinically when she was taken to the electroencephalography laboratory eight hours later. After a control recording, acetazoleamide was injected intravenously. The electroencephalographic changes are illustrated in Figure 6. An initial injection of 500 mg. did not alter the high voltage slow wave pattern, although the spontaneous twitching of the extremities lessened and the patient's attention span became longer. Thirty-seven minutes after the first dose, another 500 mg. of acetazoleamide was given intravenously. Within eight minutes, a definite alteration of the electroencephalogram was noted. The amplitude of the waves diminished, and the frequency increased from a range of 2½ to 4 to 5 to 7 cps. The improvement in the electroencephalogram persisted.

At the end of the recording, one hour after the first dose of acetazoleamide, the patient was oriented in all spheres and for the first time that day could name her physician. Her attention span was improved, and she carried out relatively complex tests of coordination. The spontaneous twitching was gone, but the flapping tremor persisted, although it was decreased in amplitude and frequency. The tendon reflexes were only slightly hyperactive, and only unsustained clonus was found at the right ankle. The plantar response on the right was suggestively extensor, while that on the left was definitely flexor. The serum sodium at the end of the examination was 118 mEq. per liter.

The patient started a profuse diuresis on the day after the acetazoleamide study, and her neurologic status showed steady improvement. Twelve days after operation, the serum sodium was 145 mEq. per liter and the neurologic examination was unremarkable.

DISCUSSION

Several workers have studied the effect of acetazoleamide on the central nervous system. Originally, it was believed that the anticonvulsant effects were indirect and due to the metabolic acidosis that resulted from increased renal excretion of sodium bicarbonate.[7] This hypothesis was contradicted when Millichap, Woodbury, and Goodman[8] demonstrated that nephrectomy did not alter the effectiveness of acetazoleamide in raising the electroshock seizure threshold of rats. Further studies demonstrated a direct relationship between the elevation of seizure threshold and brain carbonic anhydrase inhibition. Acetazoleamide, by inhibiting the enzyme carbonic anhydrase, impairs the transport of metabolic carbon dioxide from cells to the lungs. Both Mithoefer's[9] data and the present experiments demonstrate

a fall in alveolar pCO_2 after injection of the drug. Mithoefer's data indicate that tissue CO_2 concentration actually rises when carbonic anhydrase is inhibited. Several things suggest that acetazoleamide exerts its effect on the central nervous system by increasing the carbon dioxide concentration of nerve cells. Carbonic anhydrase inhibition is the only known pharmacologic action of acetazoleamide.[10] The drug raises the electroshock seizure threshold of rats in a manner identical to that of inhaled carbon dioxide,[11] and the alterations in the electroencephalogram produced by lowering blood carbon dioxide through hyperventilation are prevented by acetazoleamide.[12] The drug's effect on neuronal carbon dioxide concentration may alter the extracellular : intracellular sodium ratio, thus changing the excitability of the neuron. However, in our experiments, acetazoleamide was effective in animals with both high and low serum sodium concentrations, and specific conclusions concerning ion changes across the cell membrane cannot be drawn.

Clinical disturbances in water and electrolyte balance produce impairment of neurologic function which responds slowly to the conventional methods of treatment. Hypernatremia, caused by diarrhea in the infant, presents a particularly difficult problem in treatment, since correction of the hypernatremia with glucose water or hypotonic electrolyte solutions frequently precipitates convulsions. Acetazoleamide promptly improves the electroencephalographic abnormalities caused by experimental hypoosmolality and hyperosmolality. Its effectiveness in improving neurologic function in a case of encephalopathy due to H_2O excess has been demonstrated. Its greatest usefulness may be in preventing seizures during the treatment of hypernatremia.

SUMMARY

Alterations in the electroencephalogram were produced in 16 cats by either acute overhydration induced with intravenous glucose water solutions or hypernatremia induced with intraperitoneal hypertonic sodium chloride instillations. Both overhydration and hypernatremia caused diffuse high voltage slow activity and intermittent sharp waves in the electroencephalogram. When hypernatremic animals were acutely hydrated, the sharp activity in the electroencephalogram was increased. In all 3 states, intravenous acetazoleamide rapidly returned the electroencephalogram to normal.

When acetazoleamide was administered to a human patient with encephalopathy caused by overhydration, both her clinical status and electroencephalogram promptly improved.

Acetazoleamide appears to affect central nervous system function through decreasing the rate of transport of metabolic carbon dioxide from brain to lung, thus increasing the carbon dioxide concentration in the cell. A specific effect of the drug on the extracellular : intracellular ratio of sodium in neurons has been postulated by others, but the equal effectiveness of the drug in both hypoosmolar and hyperosmolar states reported herein does not support this concept.

Although the specific neuronal effects of acetazoleamide are not known, the drug is useful in the treatment of encephalopathies caused by water and electrolyte imbalance and merits further clinical trial.

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Familial occurrence of focal temporal electroencephalographic abnormalities

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IN THE PAST, it has been stated that genetic factors are operative in determining normal as well as certain types of abnormal electroencephalograms. The strongest conclusion about normal electroencephalograms was reached recently by Vogel[1] who stated that the electroencephalogram is, under normal circumstances during the waking-resting state as well as during sleep, completely determined by heredity. He noted[2] also that a variant of normal electroencephalograms, the flat electroencephalogram, seemed to be inherited on a simple autosomal dominant basis. The largest series dealing with the transmission of abnormal electroencephalograms were collected by Lennox, Gibbs, and Gibbs[3] in this country and by Harvald[4] in Denmark. After examining close and distant relatives of epileptics, the workers in the two countries reached similar findings. The relatives of epileptic patients showed "dysrhythmia" much more frequently than did the average population. They also noted that dysrhythmic records were more often found in women than in men. Lennox, Gibbs, and Gibbs felt that dysrhythmia might prove to be a dominant genetic trait. Harvald postulated that the greater incidence of dysrhythmia in females might be due to genetic sex linkage. Davidson and Watson[5] presented evidence recently that certain patients with photoepilepsy have relatives who also are light sensitive electroencephalographically.

Genetic studies dealing with pathologic electroencephalographic findings have been restricted largely to the investigation of diffuse electroencephalographic abnormalities. Since it is, however, a clinical observation that some patients with temporal lobe epilepsy have ancestors who likewise had a convulsive disorder that could be regarded, on the basis of the history, as having been of the temporal lobe type, it was of interest to record the parents of patients with temporal lobe seizures. It was soon apparent that the occurrence of focal temporal abnormalities in one parent was fairly frequent. Examples of this observation are shown in Figures 1, 2, and 3. A pilot study was therefore set up in order to investigate this finding somewhat further.

MATERIAL AND METHODS

The first of 3 groups of families examined consisted of the parents and siblings of children and adolescent patients from the psychiatric inpatient service of the Lafayette Clinic. The second group consisted of parents and siblings of patients with different types of convulsive disorders who were admitted to the Neurological Research Division of the Lafayette Clinic. The third group consisted of paid "normal" volunteer families. If the parents of adult epileptic patients were not available, the marital partners and children resulting from the marriages were recorded instead. After 64 families had been collected in this fashion, the first 10 families in which both parents had unequivocally normal electroencephalograms and the first 10 families in which one or both parents had temporal abnormalities were selected. The electroencephalographic records of these 84 persons were then pulled, shuffled, and numbered on the back. The only other information put on the back of the recording was the person's age. The recordings were then read independently by the authors and classified as to the presence or absence of temporal abnormalities. A rating scale was devised in which 0 meant no temporal abnormality; grade 1, mild, just discernible temporal abnormality; grade 2, definite, medium to high voltage complex or sharp activity

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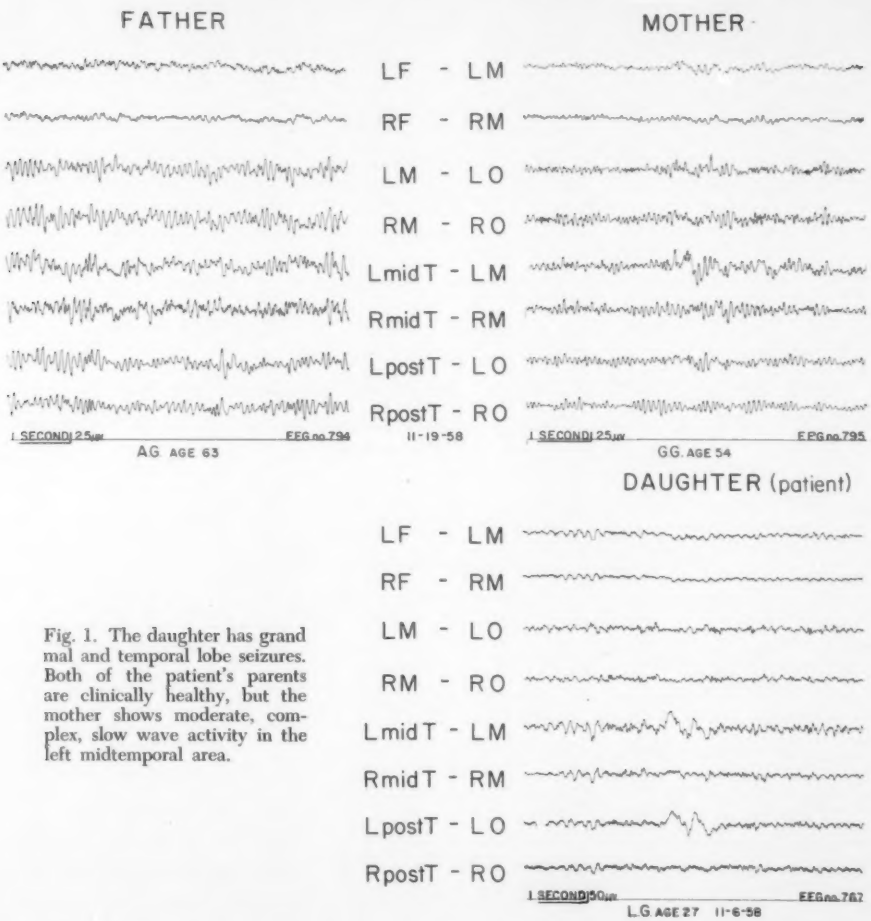


Fig. 1. The daughter has grand mal and temporal lobe seizures. Both of the patient's parents are clinically healthy, but the mother shows moderate, complex, slow wave activity in the left midtemporal area.

in the theta frequency range; and grade 3, sharp wave or spike. Figure 4 illustrates examples of the rating scale. The electroencephalographic recordings were obtained for the most part on a Grass 8 channel electroencephalograph. Some of the earlier records were obtained on a Model T Offner electroencephalograph. A total of 18 electrodes were used in monopolar and bipolar connections; 3 independent electrodes were employed on each side to record from the anterior, middle, and posterior temporal areas. The recording time was twenty-five minutes per person, which included a three-minute period of hyperventilation and a two-minute period of photic stimulation.

RESULTS

In 5 instances, there was a difference of 1 grade between the 2 observers in classifying a temporal abnormality as being grade 1 or 2, while, in 3 instances, there was a 1-grade difference between 0 and 1. No differences were greater than 1 grade. The lower values were chosen in cases of disagreement. If one observer had rated a temporal abnormality as

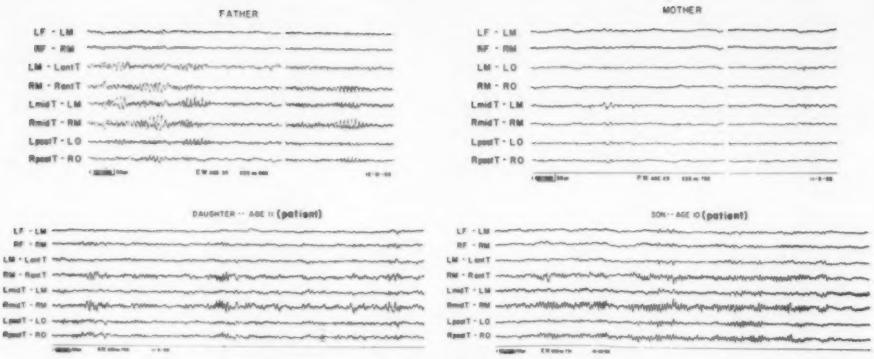


Fig. 2. Both parents are clinically healthy, although there is psychiatric illness on both sides of the family and unusual personality traits are present in both parents but no seizure disorders. The son and daughter both have marked psychiatric problems but no seizure disorders. Note the similarity of the type of abnormalities in the father and children.

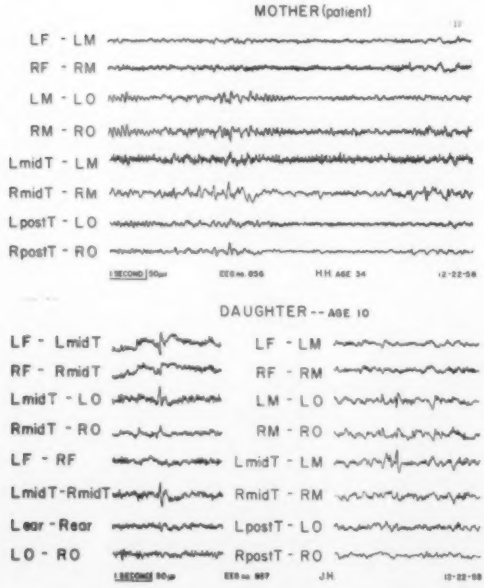
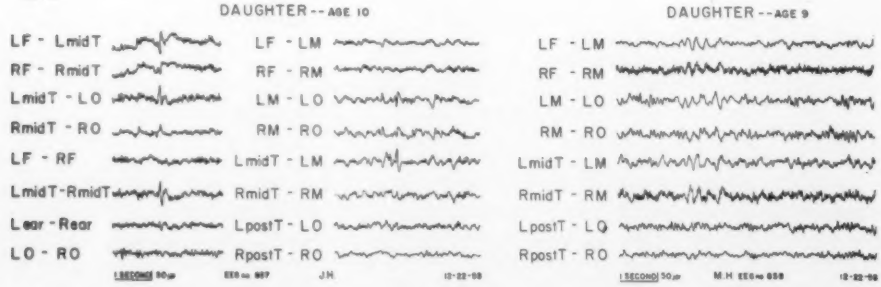


Fig. 3. The mother has grand mal and temporal lobe seizures. The older daughter is clinically healthy, while the younger daughter had one febrile convulsion in infancy.



0 and the other had rated it as 1, it remained 0. If there was disagreement between values 1 and 2, grade 1 was chosen. Findings in the group in which one or both parents had temporal abnormalities are shown in Table 1; findings in the group in which both parents had normal electroencephalograms are shown in Table 2. Number 0 refers to normal electroencephalograms T-1 to T-3, denoting varying degrees of temporal abnormalities. The letter D stands for diffuse nonparoxysmal electroencephalographic abnormalities, and the letters

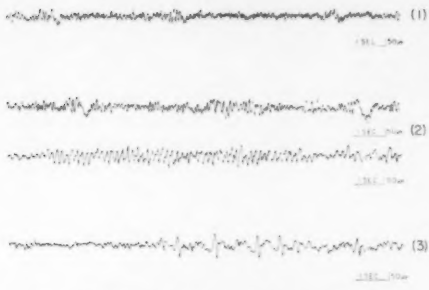


Fig. 4. Types of temporal abnormalities encountered in families. This figure shows the different grades of abnormalities as they were recorded in Table 1.

Table 1

	PARENTS		CHILDREN						
	F	M	1	2	3	4	5	6	7
1	T_2	T_1	T_2	T_2	--	--	--		
2	T_1	O	T_2	O					
3	--	T_1	O	T_1	T_1	D	O		
4	--	T_3	T_2	O					
5	O	T_1	T_3	--	--				
6	T_2	O	T_1	O	D	T_1			
7	O	T_2	O	O	--				
8	O	T_2	--	--	--	T_1	--	O	
9	O	T_2	--	--	O	--	T_1	T_3	O
10	O	T_1	T_1	O	T_1	--	--		

Table 2

	PARENTS		CHILDREN				
	F	M	1	2	3	4	5
1	O	O	O	O			
2	O	O	O	O	O	O	O
3	O	O	O	D			
4	O	O	O	O			
5	O	O	O	--			
6	O	O	O	--	--		
7	O	O	O	--	--		
8	O	O	O	O	O	O	
9	O	O	SW	--	--		
10	O	O	D	--			

SW refer to spike-wave activity. The dashes indicate family members who could not be examined. Abnormalities in temporal areas were either strictly unilateral or, more often, bilateral, independent shifting discharges.

DISCUSSION

It should be pointed out that the criteria in this investigation were purely electroencephalographic and not clinical. The parents with normal electroencephalograms do not necessarily represent normal persons or ancestors of normal persons, while parents with temporal abnormalities in their electroencephalograms are not merely parents of temporal lobe epileptics but present a variety of clinical conditions, although one family is clinically healthy. The question of whether the temporal abnormalities in this series are due to direct inheritance of the electroencephalogram or possibly due to a familial occurrence of birth injuries cannot be answered on the basis of this small series. Further investigations attempting to shed more light on this question are at present in progress. As has been pointed out, the series presented here is quite small, and it is not likely that the marked familial tendency of temporal abnormalities, as demonstrated in Table 1 in which 9 out of 10 families showed this finding, will be evident in a larger sample. The mere fact of this occurrence should be noted, however, because a practical point for clinical electroencephalographic interpretation suggests itself immediately: focal temporal abnormalities of grade 1 and, occasionally, grade 2 may bear no relation to a patient's presenting symptoms. It is quite clear that these findings occur at times on a constitutional basis in seemingly healthy persons who have not received any overt head injuries or known birth injuries.

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Experimental basotemporal epilepsy in the cat

Discrete epileptogenic lesions produced in the hippocampus or amygdaloid by tungstic acid

Baruch Blum, Ph.D., and Erich Liban, M.D.

AN EFFECTIVE WAY of producing experimental epilepsy is by the cream of alumina method of Kopeloff and associates[1,2] involving the application or injection into the brain, at particular localities, of alumina gel. With this procedure, an epileptic state resembling clinical epilepsy develops in a few weeks. The method, also used by other investigators,[3,4] served to produce various types of experimental epileptic syndrome. Thus, by injections into the basotemporal regions, two types of epilepsy have been produced, one resembling the psychomotor type, including major seizures, and the other consisting only of psychic symptoms.[4] No correlation between the exact site of injection and the syndrome produced could be noted by these investigators, since the lesions were shown to involve widespread areas at a considerable distance from the site of injection.[4]

Green, Clemente, and de Groot,[5] by inducing electrolytic lesions in the cornu Ammonis region, produced another epileptic syndrome of the psychomotor type, which showed a greater discreteness than that obtained by the alumina method. In this syndrome, a characteristic seizure pattern occurred in which the cats suddenly turned their heads to the left or right, with fixed, staring, pupillary dilation, salivation, occasional gagging, clonic twitchings spreading from the face to the limbs to the trunk, and, sometimes, tonic convulsions. This seizure pattern also seemed to include components typical of amygdaloid seizure obtained by the alumina method,[3,4,6] suggesting a lesion not restricted to the hippocampus but also involving the adjacent amygdaloid nucleus.

Production of discrete epileptogenic lesions confined to the limits of the area studied, for example, to the hippocampus or lateral amygdaloid, without penetration into adjacent structure or tracts, is of value for several reasons. It enables one to study the role of each of these individual areas usually involved in temporal lobe epilepsy, as well as the physiologic functions of these areas. It might also help the neuropharmacologist to develop rational therapeutics in the clinical disease.

In the present report, two different types of experimental epilepsy syndrome are described which can be related to very discrete lesions in the hippocampus and lateral amygdaloid nucleus and obtained by a new method.

METHODS AND MATERIALS

Epilepsy was produced by injection of minute quantities of a cold gel of tungstic acid into the hippocampus and lateral amygdaloid nucleus by the stereotaxic technic.

Cold tungstic acid gel was prepared by the gradual addition of 1 part of 5% HCl to 2 parts of 5% sodium tungstate; the product was then allowed to gel in the refrigerator. The resulting white gel was washed from residual HCl and then kept under refrigeration (6 to 7° C.) until use because of its tendency to change its physical form at room temperature. Temperature of the gel at the time of injection was 7 to 10° C.

Injection into the brain was effected with the aid of the Horseley-Clark stereotaxic appa-

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ratus (generously lent to us by Professor Jonathan Magnes of the Department of Physiology, Hebrew University Medical School, Jerusalem) ether-Nembutal anesthesia and aseptic and antiseptic conditions were utilized. The 43 adult male and female cats, weighing 3 to 3.5 kg. each, used were chosen chiefly because the size of their brains corresponded to the atlas of the cat brain of Jasper and Ajmon-Marsan,[7] which was used for the present study. For injection into the hippocampus, the coordinates chosen were frontal 8.5 and 9.0, lateral 8 and 8.5, and depth −5.5 and, for the lateral amygdaloid, frontal 9.5, lateral 11, and depth −5.5. The quantity of material injected was 0.025 to 0.03 cc. All our cats were injected unilaterally.

So that the role of low temperature in the experiment could be evaluated, cold alumina (6 to 8° C.) was injected stereotaxically into the lateral amygdaloid in 7 cats and into the hippocampus in one. Epilepsy did not appear in these animals within three days of the injection, as is usual with tungstic acid gel, but after a period of three weeks, as with alumina injected at room temperature.

For postmortem pathologic examination, the cats were anesthetized and, with their hearts slit open, their brains were perfused in situ, first by intracarotid injection of saline until the venous return from the brain became almost clear and then with 10% formalin. Steel marking needles were then introduced with the stereotaxic apparatus before the brains were removed from the skull. The brains were further fixed in 4% formalin for another one to four weeks and then sectioned, according to the markers, in frontal planes into blocks 3 mm. thick. Paraffin sections were prepared and stained with hematoxylin-eosin stain, cresyl violet, and Loyez myelin stain.

RESULTS

A well-defined type of epilepsy appeared in 19 of 31 animals in which the injection was aimed for the hippocampal coordinates. A different type of epilepsy appeared in 7 of the 8 animals in which the injection was aimed at the amygdaloid. Paroxysms started in both types of epilepsy on the second or third day after injection, and typical pathologic lesions were noted in the brains of these cats. In those cases in which epilepsy failed to appear, a stereotaxic error was usually discovered, the injection having gone into the ventricles or other adjacent structures without causing significant damage to the hippocampus or lateral amygdaloid.

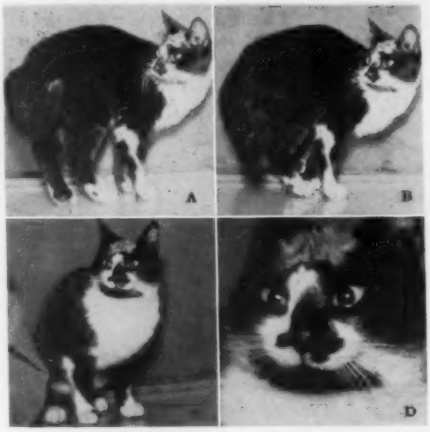

Fig. 1. Phases in a hippocampal epileptic attack. [A] Ipsiversive head turning with apprehensive and alerted facial expression. Note tonic flexion of the tail. [B] Crouched posture, gradual straightening of the head with relaxation of the tail, then successive ipsilateral, contralateral, and bilateral upper lip twitchings. Fluid salivation, nasal discharge, and pupillary dilation to 50% of full diameter. Later, loss of pupillary reactions and dilation reaches 75%. [C] Abrupt termination of the attack. [D] Drops of watery saliva, which run abundantly at end of attack, can still be seen on the left-side (contralateral) whiskers.

Paroxysmal attacks occurred for a few days. On the first day of epilepsy, the attacks initially occurred at long intervals, later becoming more frequent, every fifteen to twenty minutes; the interval slowly increased again to one or two hours and later became very infrequent in some cats, but others entered a fatal status epilepticus.

Hippocampal epilepsy. Figure 1 shows 3 phases of a hippocampal attack. Prodromal symptoms were as follows: the cat became apprehensive, standing up and sometimes also

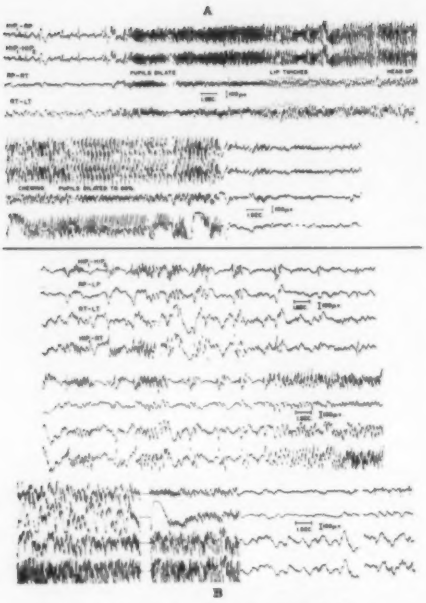

Fig. 2. Samples of electroencephalograms taken from epileptic cats with hippocampal lesions before, during, and after attacks. The cats were rendered epileptic by unilateral injection of 0.03 cc. colloidal preparation of tungstic acid into the right lower cornu Ammonis (locus of injection shown in Figure 5A and B). Bipolar recording at half the customary paper speed (see time marking). HIP_1 = deep stainless steel electrode at the epileptic focus medial to the injection locality. HIP_2 = deep stainless steel electrode similar to HIP_1, but lateral to injection locality. RP = right parietal epidural platinum-ball electrode. LP = left parietal epidural platinum-ball electrode. RT = right temporal epidural platinum-ball electrode. LT = left temporal epidural platinum-ball electrode. Symptoms are given with corresponding electroencephalographic recording in [A] (Cat: "Spike"), and a longer period of preictal recording showing many "larval" outbursts and recording from an attack are given in [B] (Cat: "Yahalom").

stretching, as if listening alertly. A few animals retched or gagged at this stage. The attacks continued with turning of the head toward the side of the lesion (Fig. 1A); the pupils dilated continuously but never reached more than 75% of their maximal diameter, even later when reaction to light was completely lost. It is interesting to note that the pupil contralateral to the side of the lesion lost its reaction to light, both direct and consensual, before the ipsilateral pupil did. As the attack further developed (Fig. 1B), the head was slowly straightened and the cat assumed a crouched posture; the pupils reached their maximal dilation, and profuse watery salivation and nasal discharge started, first appearing on the side of the mouth ipsilateral to the lesion, later from both sides, and still later from the contralateral corner of the mouth. At this later stage, in some cases, the salivation became thick. Urination sometimes occurred at this point, and clonic movements limited to the upper lip appeared first on the side ipsilateral to the lesion, then bilaterally, and, finally, contralaterally. The episode continued with motor unrest, chewing and licking movements, and profuse salivation. The attack then ended suddenly, and the animal returned to normal, except for a preoccupied expression and postictal apathy and depression (Fig. 1C and D). In some cases, lip twitching occurred ipsilaterally between attacks. No other phenomena were observed, nor was there any further spreading or generalization of symptoms in the attacks. The cats seemed to be conscious throughout regular attacks and showed great resistance and hypersensitivity to manipulation. These attacks occurred repeatedly, often for three days without change in pattern, except that, later, paroxysms of minor symptoms also appeared.

In some cases, the attacks described above continued for two to three days and then suddenly, the pattern changed, with convulsions taking place at the end of each attack. In a few cases, only minimal paroxysmal symptoms such as excitement and chewing movements occurred. These have not yet been studied in detail.

Our hippocampal epilepsy also elicited typical electrographic properties. (The electroencephalograms were made in collaboration with Professor Magnes.) Figure 2A and B shows electroencephalographic recordings from 2 different cats with hippocampal epileptogenic lesions. The recording is from depth electrodes at the focus (HIP_1) and in its close vicinity

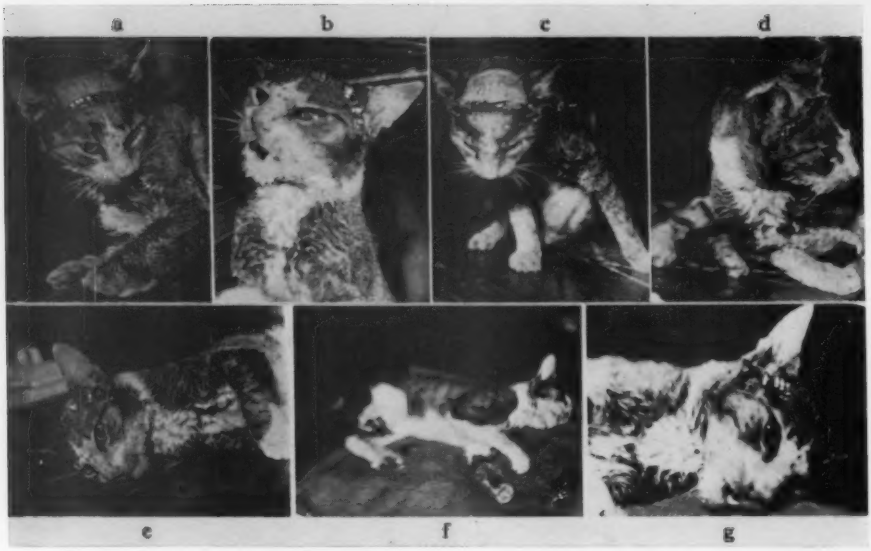

Fig. 3. Several phases of an amygdaloid epileptic attack. [a] Contraversive head turning with staring, pupillary dilation, and loss of reactions to light. [b] Salivation (thick), with chewing movements and clonus starting in mouth muscles and spreading to all other head regions and to contralateral forelimb. [c] Clonic-tonic convulsions in contralateral forelimb. [d] Convulsions become bilateral. [e] Convulsions become generalized; the cat "falls," and pupils become maximally dilated. [f] Struggling movements begin. [g] Postconvulsive exhaustion, including short-lived pupillary paresis

(HIP_2) as well as surface cortical leads. The localization of the depth electrodes is shown in Figure 5B.

Amygdaloid epilepsy. The epileptic attacks resulting from unilateral injection into the lateral amygdaloid nucleus resembled those occurring with the alumina method,[3,4,6] except that the lesions were much more discrete and the symptoms much more constant in their pattern. A typical attack consisted of the following sequence of symptoms.

Pupillary dilation occurred at the very beginning of the attack, reaching over 75% of full diameter before any other overt symptoms appeared. Contraversive head turning then occurred (Fig. 3a), and, in contrast to hippocampal attacks, pupillary dilation continued and later reached the full diameter of the pupils. Loss of the light reaction, however, took place earlier than this stage and, as in the hippocampal epileptic attack, occurred unequally in the two pupils. After the loss of the light reaction of the pupils (Fig. 3b), twitches started in the head region and were accompanied by chewing movements and running movements in contraversive direction. The convulsions developed into clonic and clonic-tonic convulsions, spreading from the head to the limbs and trunk, being first unilateral (contralateral) (Fig. 3c), and later bilateral (Fig. 3d). Thick salivation invariably occurred, and, sometimes, tonic body contortions were also seen.

During the clonic-tonic phase, the cat "falls" (Fig. 3e) struggling movements take place (Fig. 3f), and the attack terminates with postictal exhaustion and apathy (Fig. 3g). There seemed to be a loss of awareness during the convulsive episode. Minor attacks also took place, in addition to the major ones described above. The former differed in that there was no generalization of the convulsive

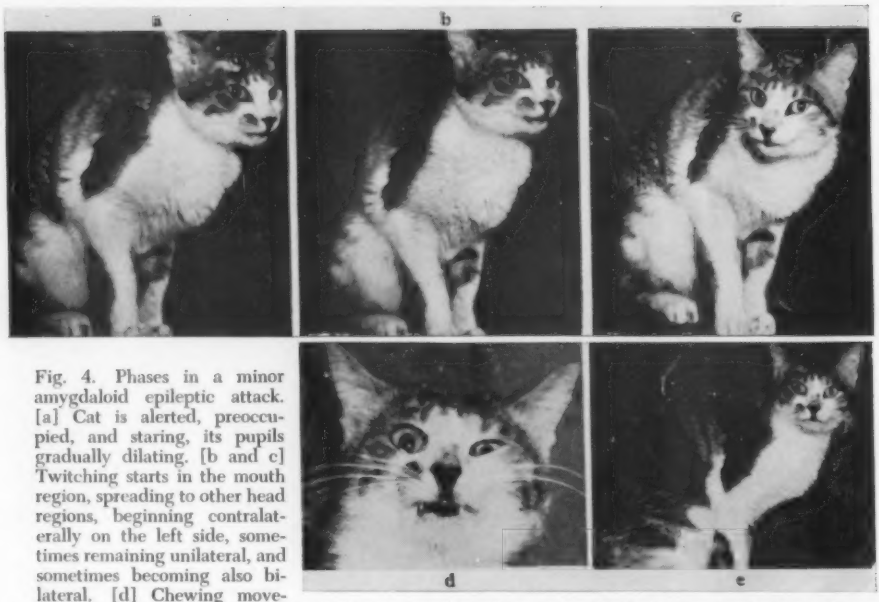

Fig. 4. Phases in a minor amygdaloid epileptic attack. [a] Cat is alerted, preoccupied, and staring, its pupils gradually dilating. [b and c] Twitching starts in the mouth region, spreading to other head regions, beginning contralaterally on the left side, sometimes remaining unilateral, and sometimes becoming also bilateral. [d] Chewing movements and twitching of left side of face (contralateral), causing palpebral narrowing on that side. [e] Abrupt termination of the attack, with disappearance of symptoms. Pupils reconstrict. No loss of pupillary reaction takes place during attack.

episode. It included partial pupillary dilation without loss of the light reaction in either pupil (Fig. 4a), staring (Fig. 4b), chewing movements, and clonus in the head region (Fig. 4c and d) occurring mainly on the contralateral side (Fig. 4d) without loss of awareness. Sometimes, these cats showed "rage" at an imaginary object during the attack, retching and gagging; 2 cats behaved as though being choked. The attack terminated suddenly but with a gradual return of pupillary function (Fig. 4e).

Macroscopic examination of the brains revealed, in most cases in which the injection was aimed at the hippocampus, characteristic lesions situated distinctly in the hippocampus and limited only to this structure (Fig. 5). However, the lesions sometimes slightly penetrated adjacent structures, such as the amygdaloid nuclei or the upper part of the pyriform lobe. In 1 cat, the injected material was found subdurally at the base of the pyriform lobe. In most of the brains in which the injection was aimed at the amygdaloid nucleus, the lesion was either confined entirely to that structure or slightly penetrated the pyriform lobe (Fig. 5c). In only 1 cat was the amygdaloid as well as the hippocampus involved.

A characteristic lesion consisted of two parts: [1] An oval, pyramidal, or irregular slit-shaped cavity, 2 x 3 or 3 x 4 mm. in diameter, with smooth or slightly rugged walls, which was empty or filled with blood or a soft, grayish material and had walls that were often composed of a thin layer of a white, firmer material simulating a capsule and [2] immediately around this pseudocapsule, a zone of about 1 mm. or more in diameter, in which the brain tissue revealed a grayish discoloration, and was of a softer consistency (Fig. 5a and b).

In addition, in most of the brains, the track of the injection needle, traversing the brain from its upper convexity, could still be seen as an hemorrhagic channel about ½ to 1 mm. in diameter (Fig. 5a and b).

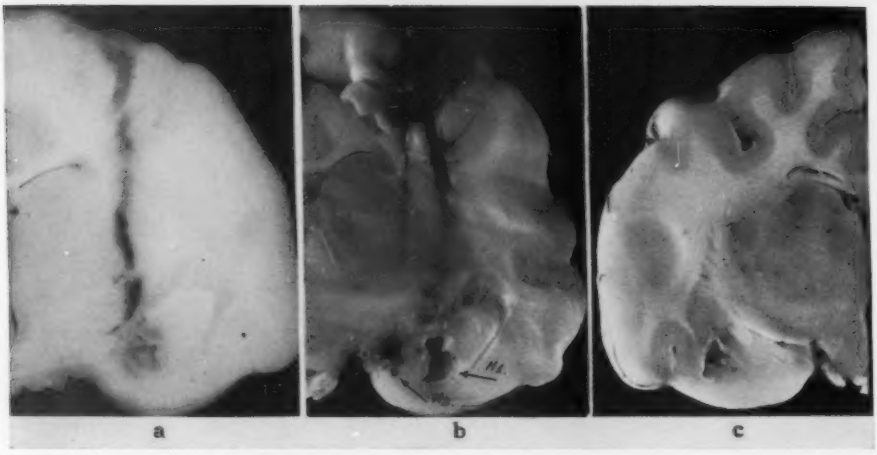

Fig. 5. Cross sections of brains of cats with epileptogenic lesions in the lower hippocampus or amygdaloid. [a] Characteristic lesion (three days old) in the hippocampus showing an irregular empty cavity well defined by a pseudocapsule. The surrounding brain tissue reveals a gray discoloration. The needle tract is seen as a hemorrhagic channel. × 2½
[b] Similar lesion (three days old) in another cat into which recording electrodes also were introduced in the vicinity of the focus. Electrode placement at the focus (HIP_1) and in its close vicinity (HIP_2), from which the electrographs of Figure 2B were recorded, is shown. × 2½
[c] Similar lesion (seven days old) in the amygdaloid nucleus which also slightly penetrates the pyriform. × 2½

On **histologic examination,** the picture varied somewhat according to the survival time of the animals. In cats killed one to three days after the injection, the cavity contained blood or small accumulations of neutrophilic leukocytes (Fig. 6A and B) and, often, irregular strands and clumps of a strongly eosinophilic homogenous material. The walls of the cavity consisted of a narrow band of structureless necrotic and compressed brain tissue, from which nerve cells had completely disappeared (Fig. 6C). In this band, various amounts of neutrophilic leukocytes were scattered, particularly at its outer border. Surrounding the cavity wall, a narrow band of edematous and/or necrotic brain tissue was noted. No leukocytic or glial reaction was seen in this second zone in cats killed after twenty-four hours, although, in those with two- to three-day-old lesions, various amounts of neutrophilic leukocytes and swollen glial cells were observed. Throughout this layer, necrotic nerve cells and many others with various degrees of shrinkage were observed. Some perivascular accumulations of microglial cells were found around some of the blood capillaries at the outside of this layer, which otherwise appeared normal.

In a four-day-old lesion, similar findings were made, except that more leukocytes were present in the cavity and the compressed layer of the wall. The surrounding necrotic layer was broader, containing many compound granular cells and swollen astrocytes (Fig. 6D). In a five-day-old lesion, the whole cavity was full of leukocytes intermingled with erythrocytes. In addition, in such brains, the pseudocapsular wall of the cavity completely vanished in some places and was narrower than usual in others.

On comparing the pathologic and clinical findings, we noted a definitive syndrome, described above as "hippocampal epilepsy," in the first group of cats, in which the lesions were confined to the medial aspects of lower cornu ammonis (Fig. 5), whereas, in those cats

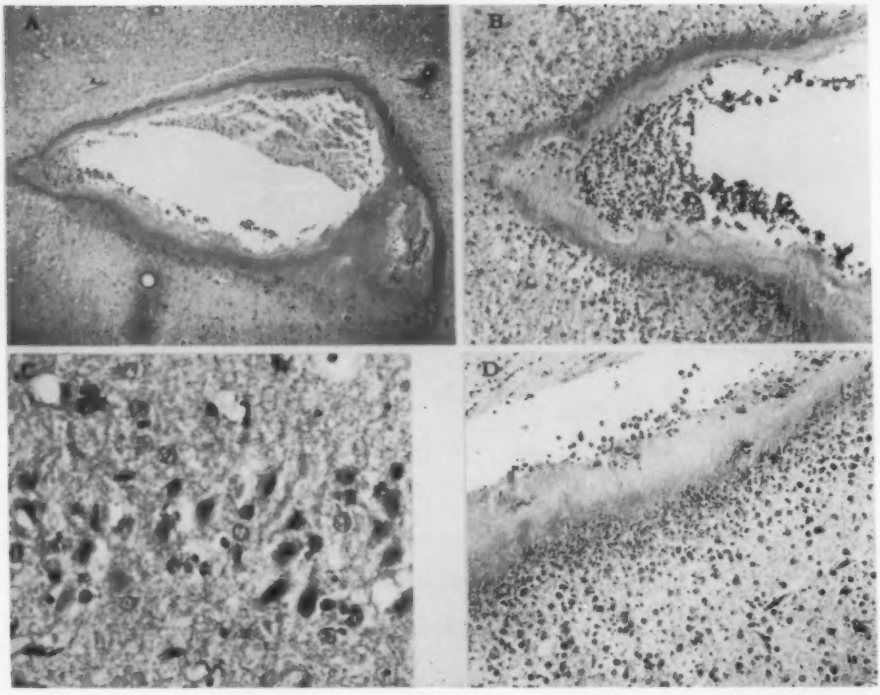

Fig. 6. [A] Lesion in the hippocampus three days after injection of tungstic acid. The wall of the cavity is formed by a narrow band of necrotic and compressed brain tissue and infiltrated at its outer border by neutrophilic leukocytes. The surrounding brain tissue reveals softening. In the cavity, blood and leukocytes present. Hematoxylin-eosin. × 33
[B] The left part of the same lesion at higher magnification × 112
[C] Necrosis and shrinkage of nerve cells of the cornu ammonis in the experimental lesion. Hematoxylin-eosin. × 360
[D] Lesion four days after injection. Many compound granular cells present in the surrounding necrotic brain tissue. Hematoxylin-eosin. × 112

in which the lesion even slightly penetrated the amygdaloid, major seizures were present as well, appearing usually on the second or third day of epilepsy. No overt differences in clinical syndrome could be detected, however, between those in which the lesion was confined to the hippocampus and those in which there was also penetration of the pyriform. In the second group of cats, with lesions in the amygdaloid nucleus only, major psychomotor seizures were observed. In one case in which the aim was the amygdaloid but the hippocampus was also involved, the cat had many minor attacks, simulating in some details the hippocampal seizures, and also major seizures typical of amygdaloid epilepsy. The attacks were more severe in cats with mixed lesions. An example of this is the last-mentioned cat, which died after one day of epilepsy.

In a few cases, due to stereotaxic error, the injection was made into the ventricle with only slight injury to rhinencephalic structures. In these, no epilepsy or only very slight paroxysmal symptoms appeared, although most of them became depressed. In the cat in which the injection was into the base of the pyriform, there were no epileptic symptoms. Only one cat with a lesion in the hippocampus and its

environs did not have epilepsy. Here, however, the damage was very extensive, so that the material might perhaps have readily escaped into the ventricle.

COMMENT

The experimental production of different "pure" forms of temporal lobe epilepsies, with definite anatomicoclinical correlation, provides a clearer picture of analogous clinical conditions, the psychomotor variants of epilepsy. Furthermore, understanding of underlying physiologic processes involved in an epileptic attack always adds to our knowledge of the physiology of the various regions of the brain involved and their interrelationship in normal and abnormal states.[8]

The hippocampus and amygdaloid nucleus are implicated in many cases of clinical temporal lobe epilepsy.[9] How these regions are involved is not yet clear.

The epileptic syndrome described here as hippocampal epilepsy is perhaps only one of several possible types of such epilepsy, since different parts of the hippocampus might harbor discrete epileptogenic lesions that could lead to different symptomatology. The term pertains to a syndrome we have observed composed of a constant pattern of symptoms, as described above, which occurred repeatedly in a paroxysmic fashion at varying intervals for days. In these, the lesions were either confined to the regions of the cornu Ammonis or included a somewhat larger section of the hippocampus in this locality. It was not produced in cats injected elsewhere nor when the lesion also penetrated parts of the amygdaloid nucleus. In the latter, the syndrome varied, as described above.

When a purely amygdaloid lesion was produced, another, altogether different syndrome of definite and constant pattern resulted. We found a significant symptomologic difference between these two sets of animals in which the two different rhinencephalic regions harbored the experimentally produced epileptogenic lesions. Some of these differences are:

1] Ipsiversive head-turning in hippocampal epilepsy, in contrast to contraversive head-turning in the amygdaloid epileptic attack. According to Kaada,[10] contraversive head-turning in an epileptic attack signifies involvement of the amygdaloid. The occurrence of this symptom at the very beginning of the attack in our amygdaloid epileptic cats and our electroencephalographic evidence for initiation of the abnormal discharge in the neighborhood of the lesion supports this contention. Ipsiversive head-turning is also known in human epilepsy,[8] but a definite correlation between this symptom in the epileptic attack and a specific region involved is now demonstrated.

2] In hippocampal epilepsy, convulsive motor phenomena did not occur in the limbs and trunk, although they did take place with amygdaloid lesions. The upper lip twitchings in the former may even be looked upon as automation rather than convulsive motor phenomena in the jacksonian sense.[10] This lack of convulsive motor phenomena in hippocampal epilepsy is interesting, especially because of our electroencephalographic evidence of the spread of the discharge to the cortical surface.

We may conclude that these two experimental types of epilepsy are of different symptomatologic composition, with only few superficial similarities.

Colloidal tungstic acid preparation and alumina gel, which produce fairly discrete epileptogenic lesions in a somewhat similar manner, have a common denominator in protein precipitation. This may be to some extent a significant factor in the epileptogenic action of both materials. This property, together with the gel form, probably plays a role in the limitation of the lesion to the vicinity of the locality of injection. This limitation is, in fact, much more successfully attained by the tungstic acid method, which produces more discrete epileptogenic lesions than the alumina method. It should be noted here that Carpenter and Whittier[11] failed to elicit an epileptic state in monkeys by application of sodium tungstate to the brain. It seems that both the physical and chemical composition of the injected material and the exact site of injection are important in the production of discrete epileptogenic foci limited to the area investigated.

The production of cystic lesions in most of our cats contrasts with both the alumina and electrolytic methods of production of epilepto-

genic foci. This feature is wanting in the latter methods and renders our epileptogenic lesions closer to those sometimes encountered in human temporal lobe epilepsy.[12,13]

SUMMARY

Based on the fact that, in temporal lobe epilepsy in man, pathologic lesions are sometimes found at the center of the focus, an attempt was made to produce epileptic foci experimentally.

In this report, two different variants of experimental basotemporal epilepsy obtained by a new method are described. Lesions in one type were confined within the limits of the cornu Ammonis at certain particular localities of this structure. In the second type, the lesions were in the lateral amygdaloid nucleus. Symptoms and electrographic recordings in the attacks, as well as the pathology of the lesion, are described.

The authors are indebted to Prof. I. Berenblum for help and advice in preparing this manuscript. We wish to thank Mr. P. Kardosh for carrying out the photographic work, Mr. B. Weisman for making the histologic preparations, and Mr. H. Otmy for technical assistance.

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The tentorial nerves and localization of intracranial pain in man

William Feindel, M.D., Wilder Penfield, M.D., and Francis McNaughton, M.D.

HEADACHE AND HEAD PAINS are perhaps among the most common symptoms with which the physician must deal. Better understanding and improved treatment of headache will depend in large measure upon extending our knowledge of the anatomy and physiology of pain-sensitive structures within the head.

Previous evidence has indicated that the dura mater is exquisitely sensitive to painful stimulation along the middle meningeal vessels and dural sinuses and at the sites where cerebral veins enter these sinuses. The innervation of these structures and their implication in dural headache were previously reported by Penfield,[1] McNaughton,[2] and Penfield and McNaughton,[3] and there is no need to cite again the literature reviewed in these reports and in those of Ray and Wolff[4] and Wolff.[5]

It may be noted, however, that the earliest written symbols for dura, from which so much head pain is derived, are found in the Edwin Smith Papyrus, which is an annotated version made in 1700 B.C. of material dating back about five thousand years.[6] The ardent bibliographer might well take this ancient series of neurosurgical cases as a starting point for his survey of the relevant literature. The hieroglyphics for meninges occur in one of the case reports describing a patient with a compound depressed skull fracture, the translation reading in part, "the smash is large, opening to the interior of his skull, (to) the membrane enveloping his brain, so that it breaks open his fluid in the interior of his head." To the unpracticed eye, the symbols appear (Fig. 1) as 2 wavy lines above 2 semicircles, followed by a symbol resembling a hammer. The neurologist or neurosurgeon, unlearned in Egyptology, might be forgiven for taking the waves to indicate cerebrospinal

Fig. 1. Egyptian hieroglyphics, the first written symbols for meninges, from the Edwin Smith Papyrus (redrawn from Breasted[6])

fluid and the hammer-like sign as symbolic of the vivid expressions applied by the patients to describe the relentless headaches for which they seek relief!

The present note is based upon a further study of the pattern of innervation of dura mater in man. Particular reference is made to the role of the tentorial nerves in head pain. The origin, course, and distribution of the tentorial nerves have been restudied. Certain anatomic details have been added to previous reports.

The fact that the tentorial nerves contain many myelinated nerve fibers of medium size is noted. It is suggested that they have functions, in addition to pain sensibility, which are as yet unknown. It is pointed out that the tentorial nerves, in contrast to the middle meningeal nerves, are related to venous rather than arterial structures.

Stimulation findings at operation have demonstrated that pain sensibility of cerebral

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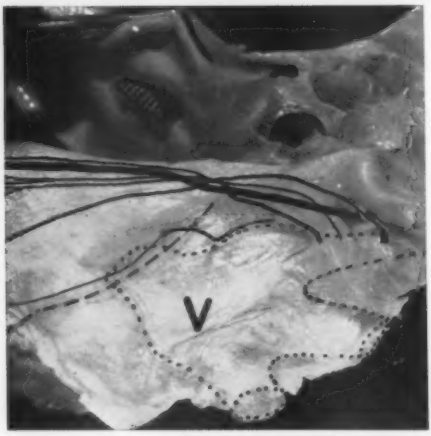

Fig. 2. Lateral view of the attachment of the tentorium to the anterior and posterior clinoid processes. The trigeminal nerve is indicated by dotted lines. The tentorial nerves and trochlear nerve (largest) are shown in black.

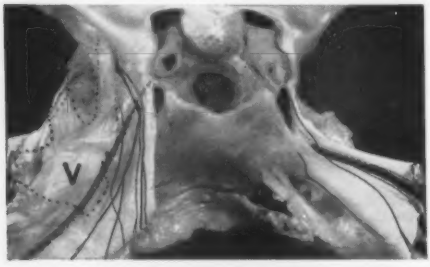

Fig. 3. Superior view of the anterior attachment of the tentorium. On the left, the outline of the trigeminal nerve is indicated by the dotted lines, the superior petrosal sinus by shading, and the tentorial nerves by black lines. On the right, the tentorial nerves and trochlear nerve are shown on the inferior surface of the tentorium.

veins entering the longitudinal and transverse sinuses is subserved by branches of the tentorial nerves coming from the first division of the trigeminal nerve. Anatomic information on the distribution of the tentorial nerves has been of practical value in obtaining more effective control of pain during craniotomy under local anesthesia.

MATERIAL AND METHODS

The study consisted of 2 parts—anatomic and surgical. For the anatomic part, the nerves in autopsy specimens of dura were stained with dilute osmium tetroxide (0.1 to 0.2%) made up in physiologic saline, the degree of staining being controlled under a dissecting microscope. The specimens were then washed, dehydrated, cleared, and kept as whole preparations in methyl salicylate.

The origin of the tentorial nerves from the ophthalmic division was analyzed in detail from a block specimen of the sella turcica, with both trigeminal ganglia and tentorial attachments being preserved. The specimen was first photographed from several views and then stained with osmium. The course of the nerves was subsequently studied and traced out on the photographs (Figs. 2 and 3).

In correlation with the anatomic findings, the second part of the study consisted of mapping out the distribution of the pain-conducting fibers in the dura mater. This was done at operation in conscious patients undergoing excision of epileptic lesions under local anesthesia. The intracranial structures being studied were stimulated by square wave pulses of 0.5 to 3 volts at a frequency of 60 cycles and a duration of 2 milleseconds. Gentle mechanical stimulation was also used. The patient was questioned regarding the localization and quality of pain. Repeat stimulations were made after local injections of 1% Novocain at selected points in the dura.

ANATOMIC FINDINGS

In the stained specimens, nerve bundles are clearly outlined in the tentorium and falx (Fig. 4). They form a plexiform pattern, continuing posteriorly toward the transverse sinus and torcular with many branches continuing up the falx toward the superior longitudinal sinus. Some dozen specimens of this type were studied, including the dura of the tentorium as well as that of the posterior fossa. In this way, anatomic information was obtained which provided the basis of a composite drawing shown in Figure 5. The course of the dural nerves going to the anterior fossa, as illustrated in this drawing, are taken directly from previous work by McNaughton, but the origin, course, and distribution of the tentorial

and middle meningeal nerves are depicted on the basis of the present anatomic specimens. As shown in this illustration, the dural nerves derived from the trigeminal nerve form the major contribution to the innervation of dural structures.

As McNaughton[2] has already demonstrated, the nerve supply of the anterior fossa is meager. A few small branches run toward the cribriform plate and upward in the anterior leaf of the falx. Several more branches of variable size and number can be traced along the sphenoid wing. All these branches come off the ophthalmic division of the trigeminal nerve.

More numerous bundles take a course across the floor of the middle fossa, to continue as a perivascular plexus about the middle meningeal artery. In monkey and man, these nerves remain closely related to the artery and its branches. Wide areas on the lateral convexity of the dura which lack arterial branches are insensitive to painful stimulation.

The most widespread of the trigeminal supply to intracranial structures is provided by the rich plexus of tentorial nerves that course back along the tentorium and sweep upward and forward in the dura of the falx. In striking contrast to the periarterial course of the middle meningeal nerves, the tentorial nerves are distributed to venous structures of the dura.

Origin of tentorial nerves. From a detailed study of a block specimen of the sella and trigeminal ganglia, it is clear that the origin of the tentorial nerves is solely from the first division of the trigeminal nerve (Fig. 2).

From 3 to 6 closely grouped branches come off the superior edge of the ophthalmic nerve and take a recurrent course posteriorly in the narrow isthmus of dura between the medial border of the trigeminal ganglion and the incisural edge (Figs. 2 and 3). Here they lie in close relationship to the trochlear nerve. The latter is often adherent to the undersurface of the tentorium and covered by a filmy membrane for a centimeter or so before it runs between the layers of dura (Fig. 3). A few tentorial nerve bundles run near the petrous attachment of the tentorium and cross over where the dura forms a roof for the rest of the trigeminal nerve. In the tentorium itself, the nerve bundles run between the 2 layers of dura, branching and spreading out to form an open plexiform pattern. They do not course intimately about the branches of the tentorial artery.

Fig. 4. Specimen of dura mater including the tentorium and posterior falx with superior and inferior longitudinal sinuses, showing the tentorial nerves stained with osmic acid

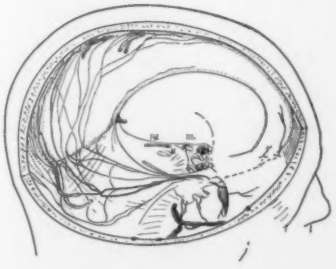

Fig. 5. Composite drawing showing the origin and distribution of the middle meningeal and tentorial nerves

Tentorial nerves to cerebral veins and dural sinuses. Nerve fibers in the walls of large cerebral veins near the dural sinuses were noted by McNaughton.[2] The origin of these nerves on veins entering the longitudinal and transverse sinuses have now been traced di-

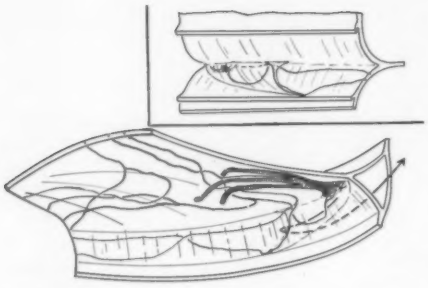

Fig. 6. Drawing to show the course of the nerve bundles on the tentorium with branches going to the occipital veins and transverse sinus. Inset shows details of nerves on a membranous flap at a venous opening into the transverse sinus.

rectly from branches of the tentorial nerves. Figure 6 shows the details of one example of this type. Some tentorial nerve bundles divide to supply an occipital vein, while others run in the free edge of a membranous valve and continue along the dural walls of the transverse sinus toward the confluence of the sinuses.

Branching of nerve bundles within the confluence of the sinuses is illustrated in Figure 7. The sinuses are depicted as opened out and viewed from their posterior aspect, the walls of the torcular having been reflected laterally and upward. This region seems to provide a focal point at which many tentorial nerve bundles converge. Some continue to arborize into smaller branches in a way that suggests their actual termination on the inner wall and the cords of Willis of the torcular.

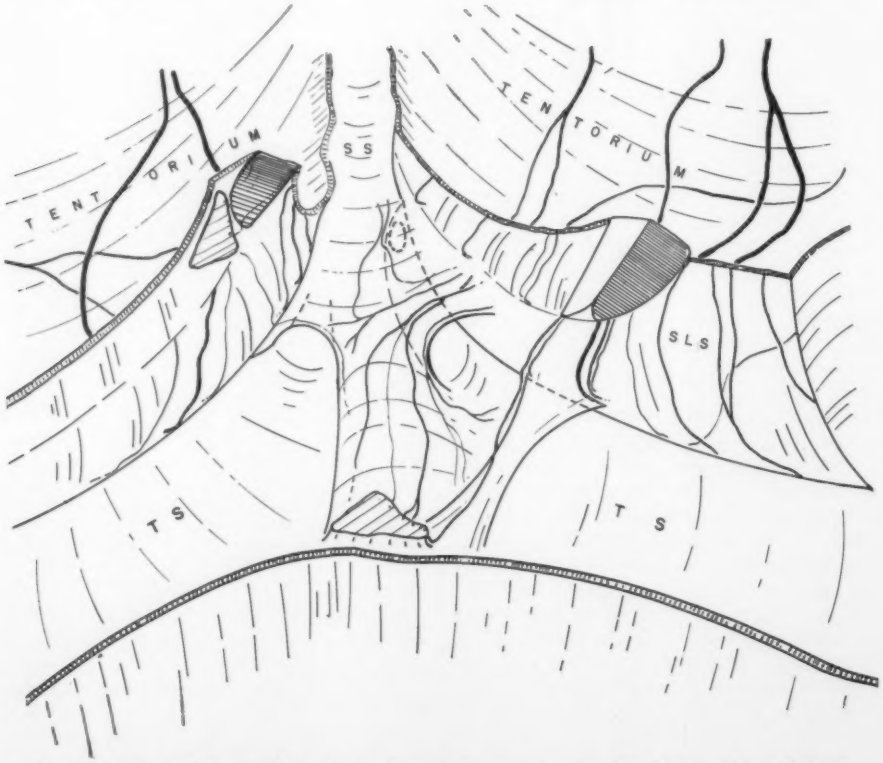

Fig. 7. Drawing of the torcular with the dura of the sinuses opened and viewed from behind: ss, straight sinus; sls, superior longitudinal sinus; ts, transverse sinus. Tentorial nerves run in the dural walls of the sinuses, and some arborize on the inner wall of the torcular.

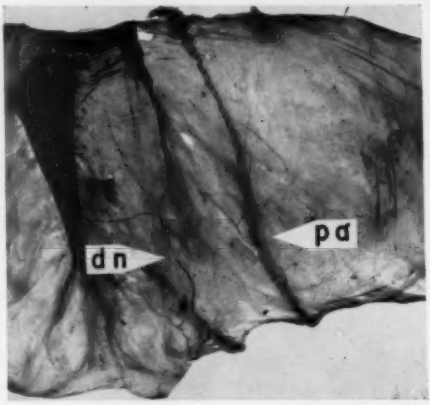

Fig. 8. Photograph of dura mater from the posterior wall of the cerebellar fossa stained with osmic acid. Dural nerve bundles (dn) run upward toward the transverse sinus. Some bundles run along the posterior meningeal artery (pa) but do not form a plexus about it.

Nerve endings in the walls of the sinuses have now been demonstrated and will be described in a separate report.

The origin of nerve fibers running along the inferior sagittal sinus has also been traced in several specimens. These can now be identified as coming from a branch of a tentorial nerve bundle that runs forward along the straight sinus (Fig. 5). Other nerves continue along the superior longitudinal sinus to the junction of

Fig. 9A. Operation photograph showing outline of occipital craniotomy.

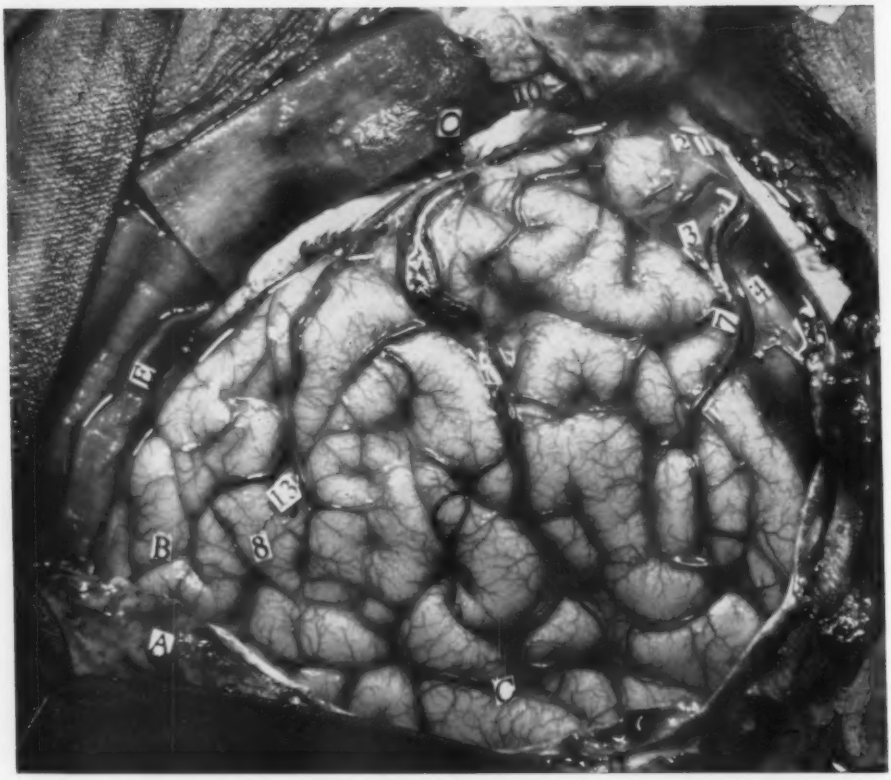

Fig. 9B. Operation photograph showing exposed occipital cortex. At 10, O and E stimulation produced pain. The leash of cerebral veins near 10 and O was also pain-sensitive.

its anterior and middle third. A few slender branches from the tentorial nerves supply the occipitoparietal dura. Here, they may overlap with the middle meningeal nerves.

Dural nerves of the posterior fossa. Some dural nerves running up from the posterior fossa also overlap with the occipital branches of the tentorial nerves (Figs. 5 and 8). They are probably derived from the ninth and tenth cranial nerves, but their precise origin still remains to be studied. Again, in contrast to the middle meningeal nerves, these nerves do not form a perivascular plexus about the posterior meningeal artery, although they may run close to it. They cross up over the transverse sinus and give off branches to the sinus walls. There is often considerable asymmetry in the number and pattern of dural nerves on either side of the posterior fossa.

On the anterior surface of the posterior fossa, the dura is supplied by branches originating mainly from the second cervical sensory root. Because of the thickness of the dura here, they are difficult to demonstrate but have been described by Rothballer[7] using a fuchsin technic involving Schiff's reagent (Fig. 14).

Summary of anatomic findings. The tentorial nerves in man are derived from recurrent branches of the ophthalmic division of the trigeminal nerve, as noted by Arnold.[8] They run posteriorly between the two layers of tentorial dura to form a conspicuous nerve plexus

that is distributed to the tentorium, torcular, falx cerebri, occipital dura, and venous sinuses enclosed by these dural septa.[9]

In contrast to the middle meningeal nerves, the tentorial and dural nerves of the posterior fossa do not form a conspicuous perivascular plexus but are related to venous rather than arterial structures.

Some nerve bundles derived from the tentorial nerves have been traced directly onto the cerebral veins draining into the transverse and longitudinal sinuses. Many other nerve branches are distributed mainly in relation to the venous sinuses themselves and can be traced as far forward as the anterior third of the superior longitudinal sinus. Nerve bundles along the inferior sagittal sinus have now been identified as coming from tentorial nerve branches.

Branches from the dural nerves of the posterior fossa extend upward to supply the transverse sinus and the occipital dura.

DURAL SENSITIVITY IN MAN

During the course of operations carried out under local anesthesia, the pain sensitive structures were defined by electrical or mechanical stimulation. Local injections of novocain were then made into appropriate regions of the dura in order to block the sensory nerves to these structures. Several examples will be described.

Case 1 (R.S.). The site of the operative incision for right occipital craniotomy is shown in Figure 9A. As shown in the photograph of the exposed brain (Fig. 9B), the prominent cortical vein just lateral to letter O was painful to electrical stimulation. Stimulation of the longitudinal sinus at points E, O, and 10 was reported by the patient to give pain referred to the top of the head. A cubic centimeter of 1% Novocain was then injected between the layers of the falx cerebri posterior to the sensitive points. The patient reported pain behind the right eye during the injection. After this, the vein and 2 of the 3 points on the dural edge were reported as no longer causing pain on stimulation. A second injection more posteriorly in the falx caused pain referred to the forehead on the same side. After this, point E was no longer sensitive. Traction of a vein entering the transverse sinus also produced painful sensation referred to the right forehead.

The results are summarized in Figure 10. The black dots represent the sensitive points, and the sensitive veins are also outlined. The larger circles represent the approximate area of the falx involved by the injection of Novocain, which caused the structures to become insensitive.

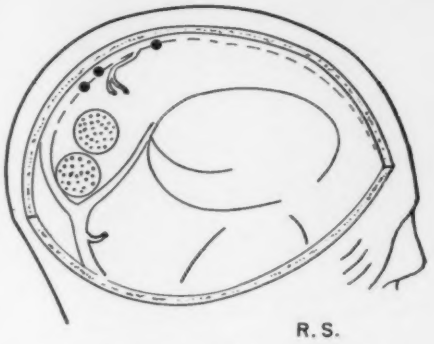

Fig. 10. Stimulation findings noted in case R.S.

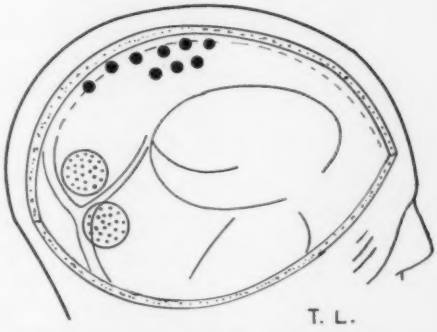

Fig. 11. Stimulation findings noted in case T.L.

Case 2 (T.L.). In this patient, the sensitivity of points along the superior longitudinal sinus and on the falx in the parietooccipital region was abolished by injection into the posterior part of the falx and the region of the torcular. After the injection, however, pressure or traction on the superior longitudinal sinus produced pain referred to the forehead or the back of the head on the opposite side. In this instance, the most anterior of the sensitive points was identified as being opposite the motor cortex. The findings are summarized in Figure 11. The persisting reference of pain to the opposite side of the head suggests that the Novocain in the tentorium was blocking most of the ipsilateral dural nerves, while the Novocain in the falx failed to block some of the sensory branches from the opposite fifth nerve.

Case 3 (G.O.). The sensitivity of a lateral lacuna and the veins related to it was abolished by local injection posteriorly in the falx cerebri. The

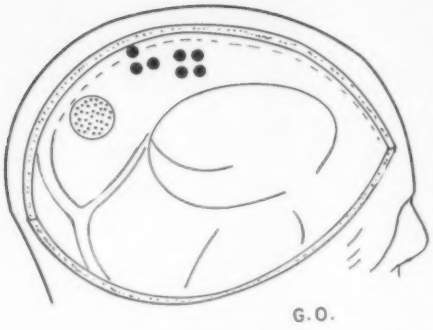

Fig. 12. Stimulation findings noted in case G.O.

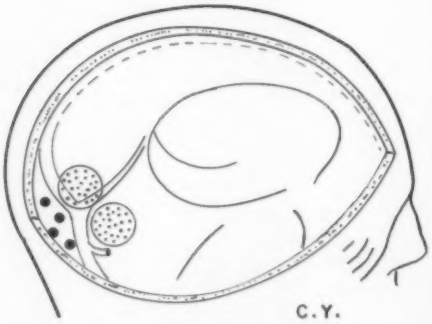

Fig. 13. Stimulation findings noted in case C.Y.

falx itself and the cut edge of the dura anterior to the site of injection were also rendered insensitive, as indicated by the black dots on the diagram (Fig. 12).

Case 4 (C.Y.). The occipital dura, meningeal adhesions above the transverse sinus, and a vein running from the occipital pole to the transverse sinus were stimulated. In each instance this produced pain referred to the region of the eye on the same side. These structures became insensitive after injections of the posterior angle of the tentorium as shown in Figure 13.

Comment on operative findings. From these results, it can be concluded that the sensitive structures noted above are supplied by afferent fibers running in the tentorial nerves to the ophthalmic division of the trigeminal nerve. A useful site for injection is evidently at the posterior and medial angle of the tentorium or the posterior angle of the falx cerebri, where the tentorial nerve bundles are to some extent concentrated.

From a practical point of view, regional dural anesthesia in these cases has been of value in effectively blocking the pain pathways from the exquisitely sensitive structures near the superior longitudinal and lateral sinuses. These structures may then be more readily dissected for exposure of the mesial cortex of the parietooccipital region. It should be noted that these midline structures along the superior longitudinal sinus were isolated from the middle meningeal nerves when the dural flap was divided and reflected. Their sensibility, therefore, is not due to middle meningeal innervation.

PAIN FROM CEREBRAL VESSELS

Manipulation of the middle cerebral arterial branches during temporal lobe excision under local anesthesia may produce pain in many patients, usually referred to the ipsilateral temple. Occasionally, the pain is referred to the region of the ipsilateral eye. The sensitivity of these patients can be abolished by injection of Novocain into the trigeminal ganglion. Here again, the first division seems implicated. In 1 patient, analgesia in the second and third divisions did not abolish the painful response. Further injections giving complete analgesia in all 3 divisions were followed by insensitivity of the middle cerebral vessels. In another patient, relief of pain coming from traction on veins of the middle fossa was obtained by injection into the ganglion, which did not, however, involve the second or third divisions insofar as sensation on the face was concerned. These findings indicate, therefore, that the first division of the trigeminal nerve also seems implicated in pain sensation from the middle cerebral vessels.

It should be pointed out that the source of innervation to the vessels of the circle of Willis is still uncertain anatomically. The nerves have not been traced from the fifth ganglion to the circle of Willis, and it is, of course, possible that Novocain injection into the region of the ganglion might well be blocking branches other than trigeminal branches, for example, within the walls of the cavernous

sinus. This particular point requires further study.

CONCLUSIONS

The rich plexus of dural nerves, derived from the ophthalmic division of the trigeminal nerve and called by Arnold[8] the tentorial nerves, forms a major contribution to innervation of intracranial structures. In contrast to the middle meningeal nerves, the tentorial nerves are related to cerebral veins and dural venous sinuses rather than arterial structures.

Evidence from both anatomic studies and stimulation responses at operation indicates that the innervation of cortical veins entering the lateral and superior longitudinal sinuses are derived from the tentorial nerves coming from the first division of the trigeminal nerve. Local anesthetic solution injected into the dura of the falx and torcular regions abolishes pain from stimulation of these venous structures. Pain induced by traction of the venous structures of the middle fossa and by traction on the middle cerebral arterial vessels can be relieved by injection of Novocain into the trigeminal ganglion. There is some evidence that, here again, the first division of the trigeminal nerve is mainly implicated. The fact that many of the dural nerve fibers are myelinated, with a diameter of 2 to 6 microns, suggests that they subserve some function other than pain sensibility. Their close anatomic relationship to venous structures indicates that they may serve as afferent nerves contributing to vasomotor function.

In view of the derivation of the tentorial nerves from the ophthalmic division of the fifth nerve and their distribution to structures other than the tentorium, the term "recurrent ophthalmic nerves," as originally suggested by Henle, might well be used. Nocuous stimulation of these nerves inside the head gives pain referred to the eye or forehead corresponding to the regions supplied by the main cutaneous branches of the ophthalmic division of the trigeminal nerve. Injection of anesthetic agent into the dura supplied by the tentorial nerves or into the trigeminal ganglion itself in the middle fossa serves as a valuable adjunct in carrying out intracranial procedures under local anesthesia. The effectiveness of these injections appears to depend upon blocking the sensory nerve fibers of the ophthalmic division of the trigeminal nerve.

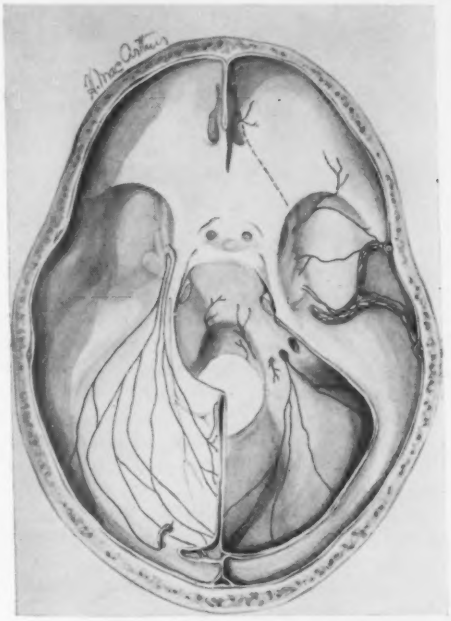

Fig. 14. Drawing to illustrate the dural innervation, based on the findings of Penfield and McNaughton,[2] with additions from the present study

The anatomic part of this study was carried out while Dr. Feindel was a graduate medical fellow of the National Research Council of Canada.

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Studies in sodium exchange

Experiments with plasma, cerebrospinal fluid, and normal, injured, and embryonic brain tissue

Louis Bakay, M.D.

THE EXCHANGE of radioactive sodium between plasma and cerebrospinal fluid has been the subject of many investigations. Much less is known about the exchange of sodium between these fluids and the brain tissue proper. The purpose of the experiments described here was to obtain information on the spatial aspect of sodium exchange between plasma and cerebrospinal fluid and normal and injured brain tissue.

MATERIAL AND METHODS

The experiments were performed in 20 cats. In the first group (10 cats), 2 cc. of 0.9% NaCl containing 50μc. of Na^{24} per kilogram of body weight was injected into the femoral vein. In 5 of these animals, cerebral lesions were induced thirty minutes to two hours before administration of the isotope. The lesion consisted of heat coagulation by puncture of the parietal cortex with a hot needle. All lesions were outlined by vital staining, 3 cc. of a trypan blue solution having been injected intravenously.

In the second group (5 cats), Na^{24} was injected intracisternally. The experimental technic consisted of slow removal of 1.5 cc. of cerebrospinal fluid through the needle into a syringe that contained 0.1 to 0.2 cc. of Na^{24} solution (2 to 4 μc.). This mixed solution was then slowly reinjected into the cistern. The barbotage was repeated once more, and 1.5 cc. of the solution was introduced into the cistern. The excess of 0.1 to 0.2 cc. was used to determine the initial radioactivity. In addition to promoting a relatively even mixing, this method also helped to avoid changes in sodium concentration of the cerebrospinal fluid. This ranged between 150 and 155 mEq. per liter in the original fluid and between 147 and 155 in the final fluid, eight to one hundred sixty minutes after injection. In a small group of controls (3 cats), Na^{24} was simply introduced into the cisterna magna as a replacement for 0.5 cc. of cerebrospinal fluid that was previously withdrawn and discarded.

In 2 cats, circular craniotomy was performed over the top of the head and bilateral dural flaps were fashioned so that equal surfaces of both parietal lobes were exposed, separated by the sagittal sinus. Lesion was produced on one side; the other side served as normal control. Afterward, 1.5 to 2 cc. of Hartman solution containing 10 μc. of Na^{24} was applied directly over the exposed surface.

The animals were killed at various intervals from eight minutes to five hours by intravenous Nembutal or intracardiac injection of 0.5 cc. of concentrated formaldehyde. All removable cerebrospinal fluid was withdrawn from the cistern, and a blood sample was taken from the heart. The exposed brain covered by the dura was frozen with dry ice, removed, and kept at −20 C.; ½- to 1-mm. sections of the brain were used for contact radioautography. It was found that the radioactivity, despite the short (14.8 hours) half life of Na^{24}, was sufficient to produce adequate density in 3 times the half-life time on Kodak No-Screen x-ray film.

Small individual samples of many different parts of the brain were weighed on aluminum planchets and dried by heating; radioactivity was determined by end-window Geiger-Müller counters. In addition, homogenized, larger portions of cerebrum, cerebellum, midbrain,

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pons, and medulla, as well as the tissue fluids, were analyzed in gamma well counters.

In those experiments in which the radioactivity of the entire brain had to be determined, the brain was cut across the midbrain and supra- and infratentorial parts were separately homogenized in a Waring blender. Measured aliquots of the homogenate were then counted in the gamma well counter and calculated to the original weight.

The sodium content of plasma, whole blood, and cerebrospinal fluid was determined by flame photometry. The plasma sodium averaged 144 mEq. per liter (143 to 146) and cerebrospinal fluid sodium 150 mEq. per liter (147 to 155). Brain tissue samples of about 100 mg. were weighed and ashed, using concentrated HNO_3, and their sodium content was determined with the Baird internal standard flame photometer. The average sodium content was 65 mEq. per kilogram of wet tissue in the cerebral cortex, 49 in the white matter of the centrum semiovale and frontal lobe, 56 in the midbrain, 58 in the cerebellum, and 67 in the medulla and pons.

RESULTS

Exchange of Na^{24} between plasma and cerebrospinal fluid. Radioactive sodium appears in the cerebrospinal fluid at a steadily increasing rate after intravenous injection. It amounts to 25% of the plasma concentration in twenty minutes, 50% in one hour, and over 80% in five hours (Fig. 1).

Na^{24} uptake by the brain after intravenous administration. Na^{24} is taken up by the central nervous tissue gradually and at a steadily increasing rate. The specific activity of that part of the brain which concentrates the greatest amount of Na^{24} is still only 60% of that of the plasma five hours after the injection. The greatest amount of Na^{24} and the only significant concentration of the isotope in the first thirty minutes is seen in the most superficial layer of the cortex as well as in the lining of the ventricular system. This indicates a rapid sodium uptake along the entire external and internal surfaces of the brain. The initial difference in specific activity between the superficial layers of the cerebral cortex and the white matter of the centrum semiovale changes with time, and a near equilibrium between these tissues is established in five hours (Fig. 1).

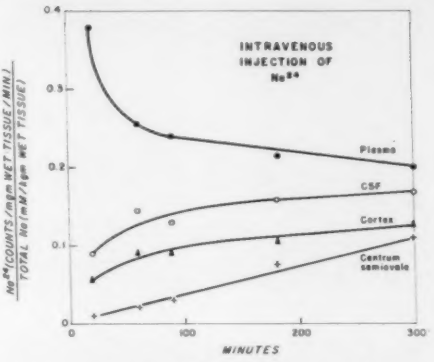

Fig. 1. Specific activity of plasma, cerebrospinal fluid, and brain after intravenous administration of Na^{24}, obtained from 5 normal cats without brain injury. Each plotted point represents the average of 3 determinations.

A study of the regional concentration of Na^{24} in the brain (Table 1) bears out this point. It also shows that all parts of the central nervous system increase their Na^{24} concentration with time, although at different rates, since added to the general uptake of

TABLE 1

Na^{24} CONTENT OF VARIOUS PARTS OF THE BRAIN AFTER INTRAVENOUS INJECTION

Time (minutes)	*20*	*70*	*90*	*180*	*315*
Plasma	35	37	36	28	29
Cerebrospinal fluid	14	22	20	25	25
Choroid plexus	14	10	7	6	8
Frontal cortex	2	4	5	5	8
Frontal white matter	0.6	1	2	3	6
Parietal lobe					
1 mm. from surface	3.5	5.0	5.0	6.2	7.9
2 mm. from surface	1.9	3.6	4.1	5.0	7.7
3 mm. from surface	0.6	1.6	2.3	3.0	6.3
Centrum semiovale	0.4	1.0	1.8	4.1	5.6
Ventricular wall	4.6	4.3	4.6	5.0	7.9
Midbrain, surface	3.2	3.8	5.2	4.5	9.1
Midbrain, depth	0.4	2.7	3.7	4.0	7.0
Cerebellum					
1 mm. from surface	2.8	4.1	5.2	8.5	11.4
2 mm. from surface	1.5	2.7	4.1	6.0	7.6
3 mm. from surface	0.4	1.1	1.4	3.2	6.2
Medulla	1.9	4.3	4.1	8.5	9.3
Lesion	45	50	28	16	26

Values are expressed in counts per minute per milligram of tissue.

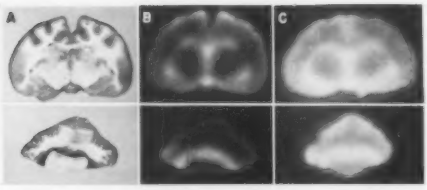

Fig. 2. Cross sections of cerebrum and cerebellum [A] and corresponding radioautography sixty minutes [B] and three hundred minutes [C] after intravenous injection of Na^{24}. White areas represent high radioactivity.

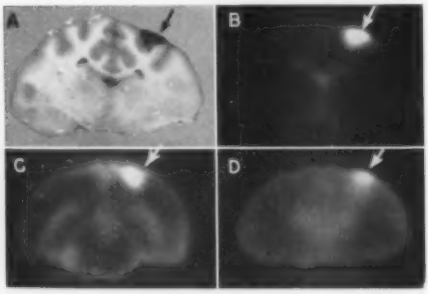

Fig. 3. Transverse section of the brain [A] and corresponding radioautographs twenty-three minutes [B], seventy minutes [C], and three hundred fifteen minutes [D] after intravenous injections of Na^{24}. The selective accumulation of the isotope in vitally stained lesions (arrow) decreases with the lapse of time.

sodium is a gradual equilibration between superficial and deep structures. The choroid plexuses are different; their Na^{24} concentration reflects the prevailing plasma level and declines with the lapse of time.

The variations in Na^{24} content of different parts of the brain are too consistent and long-lasting to be explained by the variable amount of blood included in the tissue samples, as suggested by Olsen and Rudolph.[1] Radioautographs (Fig. 2) show that the areas of highest Na^{24} concentration do not correspond to the pattern of greatest vascularity known from anatomic measurement of regional capillary population and the latest determinations with inert radioactive gases[2] and I^{131}-labeled serum albumin (RISA).[3]

Calculations on the possible influence of blood content on the radioactivity of the tissue samples gave the following results. It has been assumed that the total blood content of the cerebral cortex is not more, and possibly less, than 3% by weight of tissue. The blood in small cerebral vessels has a hematocrit of about 20%.[4] The 20% of volume occupied by the red blood cells has been included in the calculation, but it hardly increases the radioactivity of the tissues. Although the red corpuscles of the cat contain large amounts of sodium (100 mM. per kilogram), only 10 to 15% of this intracellular sodium exchanges with plasma sodium within one hour.[5] Calculations based on these data revealed that the Na^{24} content of blood included in the tissue samples did not amount to more than 30% of the radioactivity of the cortex at twenty minutes, about 15% at one hour, and negligible amounts afterward. In the deep white matter, where the initial Na^{24} concentration is very low, practically all radioactivity at twenty minutes can be attributed to intravascular sodium.

Na^{24} uptake by cerebral lesions. Cerebral lesions show a rapid exchange with plasma sodium. This results in a selective concentration of Na^{24} in the injured tissue (Fig. 3, Table 1). The ratio between the Na^{24} content of the lesion and its exact anatomic counterpart in the contralateral normal hemisphere varied between 10:1 and 15:1 within the first hour. This ratio diminished to 7:1 in ninety minutes and to 3:1 in five hours. When plotted against time, the Na^{24} content of the lesion paralleled the plasma concentration curve.

Na^{24} concentration in embryonic brain. No special study has been contemplated to observe the penetration of Na^{24} into embryonic brain tissue, but data obtained in a pregnant animal were used to compare the radioactivity in embryonic and maternal organs. This cat was killed five hours after intravenous injection of Na^{24}, and maternal blood and tissues were studied, as well as those of 4 of the embryos. The embryos weighed 50 gm. each and had a nose-anus length of 130 mm. They were considered as being from around the middle of the sixty-four-day-long pregnancy. This conclusion was reached by comparing the embryos with the data given by Latimer and Aikman[6] on the prenatal growth of the cat.

Radioautographs of sections of embryonic

and maternal brains (Fig. 4) and whole heads showed less density in the fetal brain. This seemed to indicate a smaller amount of Na^{24} in the fetal brain and is misleading because it is related to the difference in Na^{24} concentration between maternal and fetal blood. Radioautography, however, showed very clearly the completely uniform distribution of Na^{24} in the embryonic brain, with none of the difference in isotope content in various regions so typical to the adult animal. Even the large embryonic choroid plexuses were undistinguishable from the radioactivity of the surrounding brain tissue.

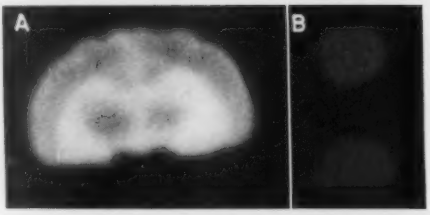

Fig. 4. Radioautographs of transverse sections of maternal [A] and embryonic [B] brains five hours after intravenous injection of Na^{24} in pregnant cat

The sodium content of maternal and embryonic plasma was equal (145 mEq. per liter). The homogenized fetal brains, however, contained 10 to 15% more sodium per unit weight than the homogenized maternal brain. This latter observation was in fairly good correlation with the increase in water content[7] and the higher chloride concentration[8] of the embryonic brain tissue.

The radioactive sodium content of the fetal plasma was only 17% of that of the mother's plasma, even at this rather late stage of five hours after intravenous injection. Flexner and Gellhorn[9] have shown that the rate of transfer of Na^{24} and other substances from mother to fetus varies a great deal from species to species and is directly related to the placental structure. The transfer rate for Na^{24} through the endotheliochorial type of placenta of the cat is actually less than 10% of that of species with a hemochorial type of placenta (man, rabbit) at the same time of gestation. When the data are corrected to the prevailing plasma Na^{24} level (Table 2), it can be seen that the embryonic brain contains about twice as much Na^{24} as the maternal brain.

Na^{24} uptake by the brain after intracisternal administration. Based on maximal withdrawal of fluid, only 20% of the original radioactivity could be recovered from the cerebrospinal fluid at forty-five minutes and 6% at one hundred sixty minutes. The plasma : cerebrospinal fluid ratio at various intervals after cisternal injection of Na^{24} was similar to that reported by Olsen and Rudolph,[1] who also applied an injection technic of slow mixing.

A considerable amount of Na^{24} injected into the cistern is taken up by the brain. Naturally, parts situated nearest to the point of injection take up disproportionally large amounts, and, in case of incomplete mixing of the isotope in the cerebrospinal fluid, they are the only parts in which Na^{24} is demonstrable. The method of barbotage distributes the tracer more evenly, as demonstrated by the following pair of experiments.

Forty-five minutes after a simple replacement of 0.5 cc. of cerebrospinal fluid with an isotonic Na^{24} solution, 30% of the originally injected radioactivity could be recovered from the cerebrospinal fluid and about 3% from the circulating plasma. The cerebellum and other structures of the posterior fossa contained 16% but the supratentorial brain less than 1%. This experiment was repeated, but with barbotage, in another animal of the same weight. At forty-five minutes, the cerebrospinal fluid contained 18% of the original radioactivity and plasma 6 to 8%. Infratentorial brain contained 7%, as did the supratentorial brain, most of the latter in the posterior parts of the cerebrum. These data not only show that Na^{24} is more evenly mixed in the cerebrospinal fluid and more evenly distributed in the brain after barbotage

TABLE 2

Na^{24} CONTENT OF MATERNAL AND FETAL ORGANS

	Mother		*Fetus*	
Plasma	33.0	100%	5.5	100%
Cerebral cortex	9.0	27	2.7	49
Centrum semiovale	6.4	19	3.3	60
Cerebellum	10.5	32	3.1	56
Liver	14.1	43	7.2	131
Kidney	13.8	42	8.7	158

Values are expressed in counts per minute per milligram of tissue.

TABLE 3

NA^{24} CONTENT OF VARIOUS PARTS OF THE BRAIN AFTER CISTERNAL INJECTION

Time (minutes)	*8*	*45*	*90*	*160*
Cerebrospinal fluid	1970	660	350	200
Plasma	0.9	5.6	4.0	6.5
Medulla	160	160	151	133
Cerebellum				
1 mm. from surface	37	40	68	74
2 mm. from surface	12	36	60	47
3 mm. from surface	3	45	36	59
Midbrain, surface	120	162	140	97
Midbrain, depth	0	24	23	54
Parietal lobe				
1 mm. from surface	3	38	8	133
2 mm. from surface	1	28	3	124
3 mm. from surface	0	9	2	91
Centrum semiovale	0	4	1	31
Frontal cortex	2	7	5	65
Frontal white matter	0	0.1	0.2	24

Values are expressed in counts per minute per milligram of tissue.

but also indicate that the rate of absorption from cerebrospinal fluid into the venous circulation is enhanced by even mixing, due to the increase of the size of the meningeal and ventricular surface in contact with Na^{24} rich cerebrospinal fluid.

One hundred sixty minutes after injection and barbotage, only 6% of radioactivity remained in the cerebrospinal fluid; 9% was in the blood and 21% in the entire brain but very evenly distributed because, of the latter, 73% was supratentorial and 27% infratentorial,

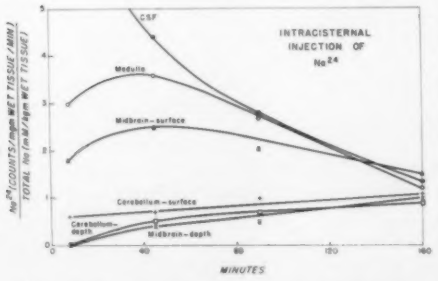

Fig. 5. Specific activity of cerebrospinal fluid and structures of the posterior fossa after intracisternal injection of Na^{24}, based on 4 experiments with identical technic of barbotage. Each plotted point represents the average of 3 determinations.

which corresponds to the difference in volume. Several cat brains were weighed, and it was found that the average of the supratentorial brain mass is 71%, compared with 29% of the weight of structures below the tentorium.

The sodium uptake by different parts of the brain depends on the evenness of mixing in the cerebrospinal fluid, as well as the time elapsed from the injection. Obviously, completely even distribution in the cerebrospinal fluid would render sodium equally available to any portion of the cortical or ventricular surface, and increasing time would allow diffusion into the deeper portions of the brain. Table 3 gives a general view of the regional exchange between brain and cerebrospinal fluid and reveals the pathways and speed of cerebral sodium diffusion. It also demonstrates that, at forty-five minutes, even the deepest parts of the brain contain some Na^{24} and that, at one hundred sixty minutes, its distribution between various parts and layers is not far from equilibrium, particularly when correction is applied for the lower sodium content of the white matter (Fig. 5). The seemingly incongruous increase in the radioactivity of the 3-mm. layer of the cerebellum in the forty-five- and one hundred sixty-minute experiments, as compared with the 2-mm. layer, is due to the nearness of the fourth ventricle, from which sodium diffuses into the cerebellum at the same rate as from the outer surface. It has to be pointed out, however, that the tabulation of data can be quite misleading in experiments of short duration when the sampling is limited to a relatively few cerebral regions. Even with the method of barbotage, it is by no means certain that the tracer is evenly distributed in the cerebrospinal fluid within the first hour; consequently, various parts of the internal and external surface of the cerebrum might be in contact with fluid compartments of greatly different Na^{24} content. Figure 6 shows an example of such uneven distribution at thirty minutes. Massive penetration of Na^{24} from the ambient cisterns into the occipital lobes can be seen, while, on the other hand, there is obviously poor mixing in the subarachnoid space of the convexity and only very scant uptake in the parietal cortex.

Diffusion of Na^{24} into the brain after direct cortical application. Sodium entered the parie-

tal cortex rapidly after the application of an isotonic Na^{24} solution over the pia-covered surface. By taking the radioactivity of the uppermost 1-mm. layer of the cortex for 100%, the second millimeter layer contained 66% and the third 37% at the end of one hundred minutes. Intra- and subcortical lesions did not take up more sodium when Na^{24} was applied in this fashion, and no significant difference could be detected between the radioactivity of the normal parietal lobe and its counterpart harboring the lesion. This finding is in agreement with experiments with radioactive phosphorus (P^{32})[10] and suggests that the blood-brain barrier is the main factor in the selective uptake of isotopes by various cerebral lesions.

Comparison of Na^{24} uptake by different routes. It must be made clear that only a rough estimation can be accomplished when an attempt is made to compare the sodium uptake by the brain after intravenous and cisternal injection. The rather late time of three hours was chosen because, by then, the mixing in the cerebrospinal fluid was complete. Consequently, the comparison was based on a time when the process of equilibration between the tissue and fluids was well on its way and the great initial discrepancies in sodium concentration had passed.

When calculated to the same concentration in plasma and cerebrospinal fluid, the brain contained almost twice as much Na^{24} three hours after cisternal injection than after intravenous injection. This is significant when one considers the size of available surface for diffusion by these 2 different routes. The total capillary surface area in cat's brain is 1,000 to 1,300 sq. cm., depending on the size of the brain.[11] On the other hand, planimetric determinations of the surface areas of the brain, based on data by Davison and Kraus[12] and including the ventricular surface, show that the entire external and internal surface of the cat's brain does not exceed 100 sq. cm. The surface area available for Na^{24} diffusion is, therefore, more than 10 times greater after intravenous injection at the time of complete mixing in the cerebrospinal fluid.

It would be very hypothetical to carry the calculations further and limit the surface areas to pore sizes, as suggested by Edström.[13] This would be irrelevant as far as sodium is concerned, since Flexner, Cowie, and Vosburgh[14] demonstrated, on the basis of Fick's law of diffusion and the rate of transcapillary exchange, that the whole wall of the capillary must be permeable to sodium, chloride, and water.

DISCUSSION

The data of these experiments concerning the exchange rate of sodium were expressed in terms of specific activity (Na^{24} per millimoles of Na), although it is known that some of the cerebral sodium, perhaps as much as 30 to 35%, is intracellular.[15,16] Previously, values on the equilibration between fluid and brain sodium were always measured in terms of saturation of the cerebral extracellular space. The size of this space, however, is not known, and even its very existence has been doubted recently.[17,18]

It is known, since the experiments of Manery and Bale,[19] that sodium injected into the

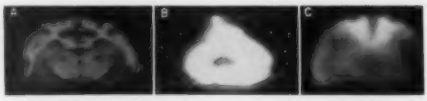

Fig. 6. Cross section of the brain [A] and corresponding radioautographs thirty minutes [B] and one hundred sixty minutes [C] after cisternal injection of Na^{24}

circulatory system does not diffuse freely into the sodium phase of the brain. The slow exchange of sodium between plasma and brain can be explained by either a delay in equilibration between cerebral extracellular fluid and plasma or the assumption that extracellular space does not exist in the brain. In the latter case, fluid as well as solutes would have to diffuse slowly through the gel-like matrix of the brain.

One might consider the cerebrospinal fluid as the extracellular fluid compartment of brain tissue and deny the existence of an extracellular space in the brain tissue itself, but 2 aspects of sodium exchange would then be difficult to explain. One would have to assume that all cerebral sodium is intracellular. In addition, the transport of every electrolyte through a cell-by-cell mechanism from the capillaries to the neurons seems to be a very

inefficient way of nutrition, as pointed out by Davson.[20]

Olsen and Rudolph[1] have pointed out that, after intravenous injection, the ratios of Na^{24} concentration of various parts of the brain to cerebrospinal fluid are about the same regardless of time. This tallies with Davson's[21] observation that the brain tissue is supplied with Na^{24} at about the same rate as is the cerebrospinal fluid. However, the experiments on which this conclusion was based did not involve detailed regional determinations or radioautography. In the experiments reported here, deeper areas of the brain definitely increased their Na^{24} concentration with time when compared with cerebrospinal fluid. The isotope content of the cortical and ventricular surface, on the other hand, maintained a fairly stable relationship with cerebrospinal fluid. The early appearance of Na^{24} along the external and internal surface of the central nervous system after intravenous injection suggests the existence of a concentration gradient with consequent diffusion of the tracer from the cerebrospinal fluid into the brain substance. Uptake by this diffusion is superimposed on the gradual process of transcapillary sodium exchange. Similar conclusion was reached by Crow.[22]

The observations on embryonic brains show that, even at the midtime of gestation, sodium exchange between plasma and brain tissue is restricted, although not as severely as in the adult animal. How much of the increased Na^{24} uptake is due to increased capillary permeability in the fetal brain and how much could be contributed by a relatively large extracellular space or the absence of myelin with its cation-binding lipids remain moot questions.

My previous work[23] with P^{32} furnishes an interesting basis for comparison of the cerebral uptake of that intracellular ion with sodium, a primarily extracellular ion. There is a striking similarity between the two as far as gradual uptake by the brain and regional distribution are concerned. This evidence supports the view that, in the complex process of electrolyte uptake by the brain, the simple distinction between intra- and extracellular ions no longer suffices. The only difference is in the speed of exchange between plasma and cerebral tissue and between various layers of the nervous tissue itself. As is to be expected, Na^{24} migrates much faster, several days being necessary for P^{32} to achieve a distribution that Na^{24} accomplishes in a matter of hours.

The similarity between the two isotopes extends to their accumulation in cerebral lesions. The only explanation of the increased concentration of Na^{24} in lesions is a local breakdown in the blood-brain barrier, since changes in cellular metabolism are not likely to involve sodium to such an extent. The lesion, being essentially a coagulation necrosis, does not include extravasation of blood that would account for its high radioactivity. Similar concentration of Na^{24} was found in brain tumors and brain edema.[24] Sodium is not fixed in the cells to any great extent, however, and the decline in time, together with the mounting radioactivity in the surrounding normal brain, results in a steep decrease of the lesion : normal ratio. P^{32}, on the other hand, maintains its selective accumulation in lesions for weeks. The negative results of Selverstone and Moulton,[25] based on a few brain tumor cases, are best explained by the delay of some hours between the injection of Na^{24} and its recovery from the brain. Their findings indicate that radioactive sodium is not suitable for brain tumor localization. They give no information on basic aspects of the barrier effect for sodium.

SUMMARY

The concentration of Na^{24} and specific activity of plasma, cerebrospinal fluid, and various parts of the brain were determined in cats by radioautography and direct tissue analysis eight minutes to five hours after intravenous and intracisternal injection, respectively.

After intravenous injection, 50% of the plasma Na^{24} concentration was attained in the cerebrospinal fluid in one hour. Complete equilibrium was not reached by five hours. The Na^{24} concentration of brain tissue revealed a slow but steady increase with time. There is a considerable delay in sodium equilibration between plasma and cerebral tissue compared with other tissues, due to the blood-brain barrier effect. Superimposed on the direct capillary exchange of sodium is evidence of additional diffusion from the cerebrospinal fluid.

The exchange of plasma and brain sodium is already restricted at the midtime of pregnancy.

The pathways and rate of absorption of Na^{24} by the brain tissue after intracisternal injection are presented. The absorption from the cerebrospinal fluid is faster than from the plasma when equal mixing of the tracer in the cerebrospinal fluid is provided for and when the data are correlated to identical concentration in the respective fluids and to absorptive surfaces of equal size.

Considerably higher amounts of the isotope were found in the injured area after intravenous injection than in the normal brain. This local increase in the permeability of the blood-brain barrier was greatest immediately after injection. It decreased rapidly with the lapse of time, but was still noticeable five hours later. The Na^{24} content of the lesion is directly related to the prevailing plasma concentration. Sodium was not taken up selectively by the lesion when applied directly over the cerebral cortex.

When the rate of cerebral uptake and the regional distribution of Na^{24}, a primarily extracellular ion, is compared with that of an intracellular ion, as represented by P^{32}, it reveals that the difference involves only the temporal but not the spatial aspects of their absorption.

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CASE REPORT

Intracranial hypertension associated with recovery of a Coxsackie virus from the cerebrospinal fluid

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INTRACRANIAL HYPERTENSION is a condition in which increased intracranial pressure occurs in the absence of a space-occupying lesion. While the descriptive terminology regarding this condition is somewhat confusing, there is reasonable unanimity concerning the essential features of the syndrome.

Established criteria[1,2] indicate that the onset is insidious, quite frequently involving previously healthy persons. Symptomatology almost always includes headache. Visual acuity may be impaired if papilledema and diplopia due to abducens palsies resulting from increased intracranial pressure persist. Less frequently, transient palsies and convulsions are noted. Physical findings are usually limited to papilledema and abducens palsies; the mental state is generally clear. The cerebrospinal fluid is under increased pressure but, with the exception of an occasional slight pleocytosis, is otherwise normal. The ventricular system is normal, and consistent electroencephalographic abnormalities have not been demonstrated. The prognosis is almost always good, the condition subsiding in a few weeks or months, although cases may persist for years and blindness secondary to optic atrophy may be a residual.

The most lucid classification of this perplexing syndrome is that of Foley,[1] who recognizes 2 major groups: [1] "otitic hydrocephalus" (". . . in which thrombosis of one or more dural sinuses following ear disease is held responsible") and [2] "toxic hydrocephalus" (with no demonstrable etiologic agent). Recognizing the term hydrocephalus as incorrect, Foley refers to the nonotitic cases as "benign intracranial hypertension" and includes under this grouping such entities previously referred to as serous meningitis, intracranial pressure without brain tumor, pseudotumor cerebri, and papilledema of indeterminate etiology.

The pathogenesis of intracranial hypertension has been the subject of extensive reviews and studies.[1–7] The origin of the cases designated "otitic" would appear to be thrombosis of dural venous sinuses, and the reversibility of the disease process is probably explained by recanalization of the thrombosed sinus. By contrast, the group designated "toxic" or "benign intracranial hypertension" is comprised predominantly of females in whom obesity is a common feature and who frequently have had nonspecific infection or mild head injury; in this group, evidence that thrombophlebitic processes are responsible is lacking. Rather, throughout the diverse literature regarding this entity runs the thread of suspicion that an infectious agent may be responsible for certain of these cases.

It is in reference to the latter group that the following case is presented.

A 22-year-old white female was admitted to the University Hospital Neurology Service for the first time on April 17, 1958, because of headache.

The patient had been well until approximately three months before admission, when she noted the gradual onset of recurrent head-

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CEREBROSPINAL FLUID STUDIES IN PATIENT WITH INTRACRANIAL HYPERTENSION ASSOCIATED WITH COXSACKIE VIRUS

Date	Opening pressure	Closing pressure	Amount	Red cell count	White cell count	Protein	Chlorides	Sugar	Culture
4-17-58	600	—	1 cc.	14	12 (100% neutrophils)	21			
4-18-58	460	300	4 cc.	14	0	20	740	58	Negative
*4-19-58	430	250	7 cc.	48	5	22	—	—	Negative
4-20-58	370	140	8 cc.	75	25 (88% lymphocytes) (12% neutrophils)	22	—	—	Negative
4-21-58	320	130	8 cc.	120	3	25	—	—	—
4-22-58	210	120	4 cc.	79	19	25	—	—	Negative
4-23-58	230	120	8 cc.	21	27 (100% lymphocytes)	34	—	—	—
4-24-58	180	114	5 cc.	240	13	32	—	—	Negative
4-26-58	200	110	6 cc.	—	—	—	—	—	—
4-28-58	210	110	8 cc.	—	—	—	—	—	—

*Indicates viral isolation

ache. The discomfort began in the morning, persisted for several days, and was described as a constant, dull ache, primarily frontal and occasionally relieved by sleep. She had occasional nausea and dizziness but no emesis, syncope, or loss of motor function. Several hours before admission, the patient noted the rather abrupt onset of numbness and tingling, involving the right face and arm, associated with ataxia of the right arm, and inability to control the movements of the right hand. However, there was no involvement of the right leg. This entire episode lasted only about fifteen minutes.

The past history was essentially noncontributory.

Examination. The patient was an alert, well-developed, moderately obese white female in no apparent distress. Blood pressure was 136/80; temperature 98.6° F.; respirations, 18; and pulse, 84. Pupils and extraocular movements were normal; both fundi revealed marked papilledema with considerable elevation and scattered hemorrhages surrounding the edema. Visual acuity was normal. Confrontation with a 2-mm. object indicated a normal peripheral extent of visual fields. Other results of the examination were within normal limits.

Cerebrospinal fluid studies are summarized in the table. Urine was normal. Hemogram showed 11,600 white blood cells per cubic millimeter with 72 neutrophils, 22 lymphocytes, 2 eosinophils, 1 basophil, and 4 monocytes; hematocrit was 42% and hemoglobin, 13.8 gm. per 100 cc. Blood urea nitrogen, blood sugar, and prothrombin time were normal. Kolmer-Wasserman and VDRL determinations were negative in both the blood and spinal fluid. Complement fixation studies for mumps, lymphocytic choriomeningitis, equine encephalitides, and St. Louis encephalitis were negative. Skull and chest roentgenograms were normal. Electroencephalogram was normal.

The patient was seen in consultation by the Neurosurgical Service; a left-sided carotid angiogram was made and interpreted as normal. The ophthalmologic consultant agreed with the impression of bilateral papilledema and reported a normal slit lamp examination. Therapy included cautious, repeated lumbar punctures. Mebaral and Diamox were given, and there was significant objective and subjective improvement. Headache disappeared after the tenth hospital day, spinal fluid pressures diminished gradually, and only slight blurring of the disk margins was noted before discharge.

Viral studies performed at the Ohio State Public Health Laboratory revealed isolation of a Coxsackie B virus, type 4, from the cerebrospinal fluid on monkey kidney tissue culture. A description of material and methods has been previously presented.[8] Since this find-

ing was reported after the patient had left the hospital, specific serologic studies were not performed and stool cultures were not obtained.

The patient was seen in follow-up study thirteen months later. Six weeks after discharge from University Hospital, she had been rehospitalized elsewhere with a recurrence of headache; lumbar puncture at that time showed "mildly elevated" spinal fluid pressure. Her headache had gradually disappeared; the patient has been free of symptoms for the past eight months and working for the past two months. Complete neurologic and ophthalmologic examinations at the time of the follow-up study revealed no residual defects.

DISCUSSION

Previous association of intracranial hypertension and isolation of a Coxsackie virus from the cerebrospinal fluid has not been found in the literature. However, the Coxsackie B viruses have been implicated as etiologic agents in pleurodynia, aseptic meningitis, meningoencephalitis, and myocarditis.

Current knowledge as to pathologic changes appearing in the human being infected with Coxsackie viruses is quite limited.[9] It has been emphasized repeatedly that ". . . diagnosis of disease caused by one of these agents [Coxsackie viruses] requires careful correlation of supporting clinical, epidemiologic and laboratory evidence."[9] Therefore, any attempt to explain the pathogenesis of intracranial hypertension, particularly on the basis of viral infection, would be pure speculation.

It is hoped that routine viral studies, particularly of the cerebrospinal fluid, in other patients manifesting this syndrome may serve to clarify the etiologic role of the Coxsackie B virus in intracranial hypertension.

The author appreciates the helpful suggestions of Dr. Dwight M. Palmer, professor of anatomy, medicine (neurology), and psychiatry, Ohio State University College of Medicine, whose patient is the subject of this report. The viral studies were performed by Dr. George Anderson of the Ohio State Public Health Laboratory.

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Correction

In the February issue, the concluding paragraph on page 215 should read: "It is postulated that [1] a highly active C_1 metabolism . . . " rather than "carbon metabolism."

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Studies in febrile seizures

IV. Evaluation of drug effects and development of a potential new therapy (Pyrictal)

J. Gordon Millichap, M.D., Patricio Hernandez, Michael R. Zales, B.S., Lawrence A. Halpern, B.S., and Bernard I. Kramer, M.D.

FEBRILE CONVULSIONS occur commonly in infants and young children, generally in response to fever caused by infections of the upper respiratory tract. It has been estimated that 1 in 50 children under 5 years of age has one or more convulsions of this type[1] and that, of febrile episodes in children under 7 years, 1 in 9 is complicated by seizures.[2] The height of the fever is an important factor in etiology, and the body temperature at onset of convulsion is a reliable measure of the febrile seizure threshold.[3] Patients with a high threshold convulse only in response to fever of 41° C. (105.8° F.) or above, whereas those who are most susceptible have seizures with fever of 38.5° C. (101° F.) or below.

Conventional methods of treatment have been found inadequate.[4] Phenobarbital, administered intermittently at the time of febrile episodes and in combination with acetylsalicylic acid or continuously in repeated daily doses, failed to prevent recurrence of febrile seizures in 48% of 40 patients treated; diphenylhydantoin given regularly and daily was entirely ineffective in 7 patients. Tepid baths and other simple antipyretic measures also were unsatisfactory. The frequency of febrile seizures in pediatric practice and the concomitant neuronal damage that sometimes occurs[5] emphasize the need for new and improved therapeutic agents.

The ideal therapy for febrile seizures should have both antipyretic and anticonvulsant effects in nondepressant doses. Since seizures occur only at the time of an acute febrile illness, the action of the drug should be rapid in onset and allow intermittent administration so that necessity for continuous medication may be avoided. The present report deals with the modification of experimental febrile seizures by various classes of pharmacologic agents and the introduction of laboratory methods for the evaluation of potential new therapies. The development of a new agent, phetharbital (1-phenyl-5, 5-diethylbarbituric acid; Pyrictal; BW No. 401), is described[6] and its properties are compared with those of conventional anticonvulsant drugs. (Pyrictal and other chemicals were synthesized and supplied by Burroughs Wellcome & Co., Inc., Tuckahoe, N. Y.)

LABORATORY METHODS

Swiss albino mice, 2 to 3 weeks of age and 15 to 20 gm. in weight, were used as experimental animals. Hyperthermia was induced by means of a microwave diathermy generator, according to the method described in a previous communication.[3] The dosage of radiofrequency energy controlled by a variable autotransformer was 60% of the maximal power output. Body temperature was recorded initially and at the onset of clonus with a telethermometer and thermistor hypodermic probe, which was inserted into the deep subcutaneous tissue of the back. The generalized clonic pattern was chosen as the onset of the febrile seizure since this was the principal component and the clearest endpoint. The duration of application of the hyperthermic stimulus to onset

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TABLE 1

EFFECTS OF DRUGS ON EXPERIMENTAL FEBRILE SEIZURES IN MICE

Drug	Route	Doses	Body temperature	Rate of rise of temperature	Threshold convulsive temperature	Severity of seizure
		mg. per kg.				
Antipyretics:						
Aspirin	Oral	10—600	0	0	—	+
Phenacetin	Oral	10—600	0	0	0	0
Antibiotics:						
Penicillin	Intramuscular	1,000—60,000 units per mouse	0	0	0	+
Terramycin	Intramuscular	100	0	0	0	+
Tranquilizers:						
Thorazine	Oral	50—600	—	—	0	0
Serpasil	Oral	20	—	—	0	+
Antihistaminics:						
Benadryl	Oral	150	0	+	—	+
Pyribenzamine	Oral	200	0	+	0	+
Vasodilators:						
Histamine	Intraperitoneal	1,500	0	0	0	—
Pilocarpine	Subcutaneous	50	0	—	0	0
Anticholinergic:						
Atropine	Subcutaneous	750	0	—	+	—
Anticonvulsants:						
Pyrictal	Oral	150*	—	—	+	—
Phenobarbital	Oral	100*	0	—	+	—
Gemonil	Oral	150*	—	—	+	—
Tridione	Oral	1,400*	0	—	+	—
Miltown	Oral	300*	—	—	+	—
Diamox	Oral	60—3,000	0	0	+	0
Dilantin	Oral	10—600	0	0	—	+
Adrenocorticoids:						
Cortisone	Subcutaneous	2.5 mg. per mouse daily x 3	0	0	0	+
DOCA	Subcutaneous	0.5 mg. per mouse daily x 3	0	0	0	—

\+ Significant increase ($P < 0.05$)
0 No significant effect
— Significant decrease ($P < 0.05$)
* ED_{50} for complete control of febrile seizures

of seizure was timed, and the rate of rise of body temperature was calculated.

Various classes of drugs were tested for their ability to [1] lower the body temperature, [2] retard the rate of rise in body temperature in the presence of the hyperthermic stimulus, [3] modify the threshold convulsive temperature, and [4] abolish the seizure completely (Table 1). Signs of acute neurotoxicity and other side effects were observed according to tests described by Swinyard.[7] Drugs administered orally were suspended or dissolved in 10% acacia in water. Each drug was tested at a number of different intervals of time or at its previously determined time of peak effect. Various doses were employed, and between 5 and 10 mice were tested at each dose level. Groups of control animals were given a volume of distilled water equal to that of the solution or suspension of drug administered to the test animals. The body temperature, rate of rise of temperature, threshold convulsive temperature, and pattern and severity of the febrile seizure were com-

pared in the control and test animals. The degree of significance of the hypothermic and antipyretic effects and of the modification of the febrile seizure threshold was estimated when possible.

Several new chemicals, derivatives of 6 different parent structures, were screened first for their ability to prevent seizures induced by electroshock stimuli and pentylenetetrazol (Metrazol); those most effective and least toxic were selected for testing against fever-induced convulsions. An electroshock stimulus of 50 milliamperes was administered for 0.2 second by means of corneal electrodes for the induction of maximal tonic-clonic seizures in mice; drugs were tested for their ability to prevent the tonic extensor component of the seizure. The convulsive dose (CD_{99}) of Metrazol in mice was 100 mg. per kilogram by subcutaneous injection; the animals were observed for thirty minutes after injection for any evidence of clonic or tonic seizures activity. Altogether, 59 new drugs were screened by a simple preliminary test. Each drug was administered orally to mice in doses of 10, 100, and 600 mg. per kilogram, and 3 animals were employed at each dose level; a total of 9 animals was used for each test procedure. The animals were observed for signs of toxicity and were subjected to electroshock stimuli or injected with Metrazol one, two, or three hours after receiving the drug. Anticonvulsant potency and toxicity of each new drug were expressed as the percentage of animals protected from seizure activity and the percentage showing minimal signs of neurotoxicity. Conventional anticonvulsant drugs were tested similarly for comparison.

Inasmuch as the measure of usefulness of an anticonvulsant drug is not its absolute potency but its therapeutic index (margin of safety), the specificity of those drugs that controlled the febrile seizure was expressed as a "protective index," which represents a laboratory approximation to the therapeutic index and is obtained by dividing the toxic dose (TD_{50}) of each drug by the effective dose (ED_{50}). The TD_{50} is that dose which causes minimal signs of neurotoxicity, such as mild sedation, ataxia, or hyperexcitability, in 50% of animals. The ED_{50} against febrile seizures is the dose required to prevent all manifestations of clonic and tonic seizure activity in 50% of animals; mice are subjected to the hyperthermic stimulus until the animal dies or a seizure occurs. The ED_{50} of the most potent and least toxic of the new compounds against fever, Metrazol, and electroshock-induced seizures were compared with those of conventional anticonvulsants. Determinations of parallelism of dose-effect lines and estimates of relative potency and toxicity were made by the methods of Litchfield and Wilcoxon.[8]

The rate of rise of body temperature was estimated in all animals used for the determination of anticonvulsant potency, and the mean value at each dose level was compared with the mean rate of rise in a control group of 8 mice subjected to the same intensity of heat stimulus as the test animals. The antipyretic effect of various doses of each drug was obtained from the difference in the rate of rise of temperature in the control and test animals; it was expressed as the per cent retardation in the rate of rise.

The movements of animals during the induction of hyperthermia were recorded with a polygraph and by means of a cage suspended from a straingauge transducer. The record obtained of the preconvulsive and convulsive movements of control mice was compared with that of mice treated with anticonvulsant drugs.

RESULTS

Effects of drugs on body temperature and fever-induced seizures. The effects of various classes of pharmacologic agents on experimental seizures induced by hyperthermia are shown in Table 1. *Antipyretics:* acetylsalicylic acid (aspirin) and acetophenetidin (phenacetin) failed to retard the rate of temperature rise, and aspirin, in doses of 600 mg. per kilogram, lowered the threshold convulsive temperature and heightened the severity of the febrile seizure. *Antibiotics:* penicillin and oxytetracyline (Terramycin) tended to increase the severity of the seizure pattern in some animals. *Tranquilizing agents:* chlorpromazine (Thorazine) and reserpine (Serpasil) were effective hypothermic and antipyretic agents but had no effect on the threshold con-

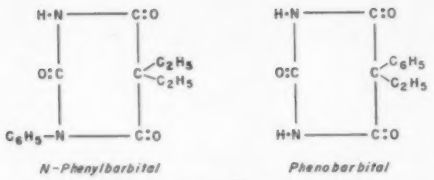

Fig. 1. Chemical structure of N-phenylbarbital (Pyrictal) compared with phenobarbital

vulsive temperature and no anticonvulsant activity. Serpasil increased the severity of the febrile seizure pattern, which became tonic extensor in type. *Antihistaminics:* diphenhydramine (Benadryl) and tripelennamine (Pyribenzamine) accelerated the rate of rise of temperature and increased the severity of the febrile seizure. Benadryl lowered the threshold convulsive temperature. *Vasodilators:* histamine retarded the rate of temperature rise but not significantly; the antipyretic effect of pilocarpine was significant. *Anticholinergic:* atropine was both antipyretic and anticonvulsant. *Anticonvulsants:* phetharbital (Pyrictal), phenobarbital, metharbital (Gemonil), trimethadione (Tridione), and meprobamate (Miltown) retarded the rate of rise of body temperature and prevented the febrile seizure; in animals unprotected by the anticonvulsants ED_{50}, the threshold convulsive temperature was elevated. Pyrictal, Gemonil, and Miltown, in anticonvulsant ED_{50}, had significant hypothermic effects. Acetazoleamide (Diamox) raised the threshold convulsive temperature but did not abolish the seizure; an antipyretic effect was observed only with doses of 3,000 mg. per kilogram. Diphenylhydantoin (Dilantin) failed to control the febrile seizure and, indeed, exacerbated the clonic pattern; the threshold convulsive temperature was reduced significantly with doses larger than 50 mg. per kilogram. Ammonium chloride and carbon dioxide were inactive in the doses employed, 500 mg. per kilogram orally and 7.5% in air by inhalation, respectively. *Adrenocorticoids:* cortisone tended to increase the severity of the tonic seizure pattern, whereas desoxycorticosterone acetate (DOCA) decreased the clonic seizure movements.

Properties of Pyrictal compared with conventional anticonvulsants. *Anticonvulsant effects.* Pyrictal was the most potent of the new compounds, and its toxicity was relatively low. The chemical structure (N-phenylbarbital) is compared with that of phenobarbital in Figure 1. Table 2 shows an approximation of the anticonvulsant potency and toxicity of Pyrictal determined by the simple preliminary screening procedure in nonfebrile animals and compared with the activity of conventional anticonvulsant drugs. The anticonvulsant effect of Pyrictal differed from Dilantin and resembled more closely that of Tridione; Metrazol seizures were controlled more effectively than those induced by electroshock. The ED_{50} of Pyrictal for the control of Metrazol seizures was 45 mg. per kilogram, whereas the dose necessary for an equivalent degree of control of electroshock seizures was 205 mg. per kilogram (137-308).

Control of febrile seizures. The efficacy of drugs against fever-induced seizures in mice was directly related to the potency of anti-Metrazol activity. Table 3 shows the anticon-

TABLE 2
ANTICONVULSANT ACTIVITY AND TOXICITY OF PYRICTAL COMPARED WITH CONVENTIONAL ANTIEPILEPTIC DRUGS BY SIMPLE PRELIMINARY TEST

Drug	*Animals protected from experimental seizure*		*Animals with toxic effects*
	Electroshock	*Metrazol*	
	%	%	%
Pyrictal	41	78	33
Phenobarbital	78	67	67
Gemonil	55	67	67
Tridione	19	33	0
Dilantin	78	0	50

See text for details of test.

TABLE 3

COMPARISON OF ANTICONVULSANT AND ANTIPYRETIC ACTIVITY OF PYRICTAL AND CONVENTIONAL ANTIEPILEPTIC DRUGS IN FEVER-INDUCED SEIZURES IN MICE

Drug (oral)	Time of maximal effect	Toxic dose (TD_{50})	Experimental seizure: Hyperthermia ED_{50}	Hyperthermia Protective index	Metrazol ED_{50}	Metrazol Protective index	Antipyretic activity
	(hour)	mg. per kg.	mg. per kg.		mg. per kg.		%
Pyrictal	1½	190 (152–238)*	150 (112–200)	1.3	45 (31–65)	4.2	18 (9–28)
Miltown	1½	275 (215–335)	310 (177–542)	0.9	103 (72–153)	2.7	24 (22–26)
Tridione	1½	1,110 (1,010–1,220)	1,380 (1,200–1,587)	0.8	620 (492–782)	1.8	12 (10–14)
Phenobarbital	3	57 (48–66)	103 (61–173)	0.6	27 (19–33)	2.1	4 (1–7)
Gemonil	1½	74 (53–104)	150 (98–221)	0.5	40 (22–72)	1.9	14 (2–27)
Diamox	3	2,000 (1,450–2,760)	—	.0	—	.0	—
Dilantin	3	110 (65–176)	—	.0	—	.0	—

*95% confidence limits

vulsant potency, toxicity, and protective index of Pyrictal in comparison with other antiepileptic compounds. The anticonvulsant ED_{50} of all drugs against febrile seizures were 2 to 3 times greater than the doses required for the control of nonfebrile Metrazol seizures, and the protective indices were correspondingly lower. Diamox and Dilantin were ineffective against both febrile and Metrazol seizures.

The anticonvulsant potency of Pyrictal was greater than that of Tridione and Miltown, equal to Gemonil, and not significantly different from phenobarbital (potency ratio [1.45]< f p.r. [1.82]).[8] The neurotoxicity of Pyrictal was significantly lower than that of phenobarbital and Gemonil and the protective index was higher and greater than 1. Miltown and Tridione were relatively less toxic but the protective indices were less than 1.

Toxic effects. Neurotoxic effects of Pyrictal were observed at dose levels greater than the ED_{50} for fever-induced seizures. They consisted of hyperexcitability and tremor in response to stimulation, and sedative effects were minimal. In mice given 300 mg. per kilogram, a dose twice the ED_{50}, spontaneous clonic jerks occurred. In a personal communication, Dr. E. J. de Beer states that, in acute and chronic toxicity studies performed at the Wellcome Research Laboratories, toxic doses of Pyrictal produced effects in rats, dogs, and monkeys similar to those found in mice; signs of hematologic and hepatic disturbance were not observed.

In graphic recordings of the movements of mice during the induction of hyperthermia, control animals exhibited exploratory behavior and later became hyperkinetic; onset of the convulsion was preceded by a short quiescent period. In contrast to phenobarbital, Miltown, Tridione, and Gemonil, the ED_{50} of Pyrictal prevented the seizure without sedation, paralysis, or depression of the normal activity of the animal. Dilantin caused exacerbation of the clonic seizure; the dose employed (50 mg. per kilogram) was approximately 5 times the ED_{50} for the abolition of the tonic component of maximal electroshock seizures in mice.

Hypothermic effects. A significant hypothermic effect of Pyrictal, observed in response to the anticonvulsant and nontoxic ED_{50}, was of equal magnitude to that of the equivalent anticonvulsant but toxic dose of Miltown (−3.0°F.; $P<0.02$). The motor system of mice treated with Pyrictal was not disturbed, whereas the animals given Miltown were paralyzed. The anticonvulsant ED_{50} of phenobarbital and Tridione showed no significant hypothermic effect; a fall in body temperature in response to Gemonil was associated with sedation and depression of activity.

Antipyretic effects. Figure 2 shows the anti-

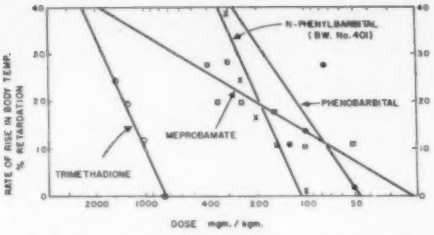

Fig. 2. Antipyretic effect of N-phenylbarbital (Pyrictal) compared with conventional anticonvulsants. × N-phenylbarbital; •, phenobarbital; □, meprobamate; ○, trimethadione

pyretic activity of Pyrictal and other anticonvulsants in animals treated with various doses and subjected to hyperthermia. In contrast to Pyrictal, Miltown, and Tridione, the activity of phenobarbital was irregular and a satisfactory dose-response curve was not obtained. The effect of Pyrictal was significant in nontoxic doses (150 mg. per kilogram) whereas phenobarbital was inactive at a toxic dose level (50 mg. per kilogram). The antipyretic potencies of the TD_{50} of these drugs are compared in Table 3. The potential value of Miltown, Tridione, and Gemonil as antipyretics was limited by the associated muscular paralysis or sedation.

CLINICAL EVALUATION OF PYRICTAL

Antipyretic activity. Pyrictal was prepared in scored tablets containing 100 and 200 mg. The drug was administered to 71 infants and children who were admitted to the Emergency Service of the Bronx Municipal Hospital with fever greater than 38.3° C. (101° F.). The fever was due principally to acute upper respiratory tract infection and otitis media or was of unknown origin. The age of the patients ranged from 3 months to 8 years. The average single dose of Pyrictal administered orally was 23 mg. per kilogram, and the range was 14 to 30 mg. per kilogram; 4 children with continuous fever who were admitted to the Pediatric Service were treated with doses of 2 to 5 mg. per kilogram initially and with larger doses on subsequent days, so that a response in relation to dose might be observed. Tepid baths and aspirin therapy were not employed. Body temperature was recorded rectally before and one hour after administration of the drug. A control group of febrile patients was observed for one hour without antipyretic therapy, and any change in the patient's temperature was recorded.

Anticonvulsant activity. The efficacy of Pyrictal was evaluated in 20 institutionalized patients with major, minor, or combined seizures previously uncontrolled by conventional antiepileptic drugs. The age of the patients ranged from 1 to 42 years; the average age was 10 years. The average daily dose was 17 mg. per kilogram divided and administered orally at intervals of four, six, or eight hours. The average monthly incidence of seizures recorded after introduction of Pyrictal and during the trial period of ten weeks was compared with the average monthly incidence during a period of thirty weeks preceding the trial. Phenobarbital, Dilantin, and primidone (Mysoline) were gradually discontinued in patients whose seizures were controlled by the new drug. Blood and urine were examined at monthly intervals.

Control of febrile seizures. The combined antipyretic and anticonvulsant properties of Pyrictal were examined in 14 infants and children who attended the Bronx Municipal Hospital with fever greater than 38.3° C. (101° F.) and had previous histories of febrile seizures. The drug was administered orally in doses of 20 mg. per kilogram at the onset of acute infection, and smaller doses were given at intervals of eight hours until the temperature was less than 38.3° C. Tepid water baths and antibiotics were prescribed as necessary. The incidence of recurrence of febrile seizures was recorded.

RESULTS

The clinical confirmation of antipyretic and anticonvulsant properties of Pyrictal is summarized in Table 4. A reduction of fever was observed within one hour in a significantly greater proportion of children treated with Pyrictal than in the untreated control group ($X^2=9.0$, $P<0.01$). An antipyretic response in relation to the dose occurred in 4 patients with continuous fever who were treated on 3 or 4 occasions. Whereas small doses of 2 to 5 mg. per kilogram were without effect, doses of 15

TABLE 4
CLINICAL EVALUATION OF ANTIPYRETIC AND ANTICONVULSANT ACTIVITY OF PYRICTAL

Indication	Pyrictal		Controls	
	Number of patients	Patients relieved	Number of patients	Patients relieved
Fever	71	53 (75%)	16	5 (31%)
Epilepsies				
Major	15	8 (53%)	15	0
Minor	10	9 (90%)	10	0
Febrile Seizures	12	12 (100%)	40	21 (52%)

See text for details. Activity of Pyrictal against fever, epilepsies, and febrile seizures is significant when compared with controls ($P < 0.01$).

to 30 mg. per kilogram were associated with a fall in temperature.

A reduction in the incidence of seizures of 75% or more was obtained in 8 of 15 epileptic patients with major seizures and in 9 of 10 patients whose seizures were minor in type. Myoclonic, opisthotonic, and absence seizures were controlled more effectively than the major tonic or tonic-clonic pattern, and a combination of Dilantin and Pyrictal was necessary for satisfactory treatment of major epilepsies. On reduction of the dose of phenobarbital, Dilantin, or Mysoline and the maintenance of Pyrictal, an exacerbation of major seizures occurred in 7 (47%) of 15 patients.

Febrile seizures did not recur in 14 patients treated with Pyrictal intermittently at onset of acute upper respiratory tract infections, whereas the incidence of recurrence was 48% in patients who had received phenobarbital and aspirin intermittently or phenobarbital continuously in repeated daily doses.[4] Between one and three febrile episodes occurred in each child during the period of observation and trial of Pyrictal. The height of the fever at the time of administration of the drug was approximately equal to that at which febrile seizures had previously occurred with similar infections.

Serious toxic effects were not observed. Examination of the blood for hemoglobin concentration and total white cells and of the urine for protein, reducing substance, red cells, white cells, and casts revealed no abnormality. Jaundice did not occur. In febrile children treated intermittently and with single doses of 14 to 30 mg. per kilogram, no side effects were observed. In epileptic patients who received repeated daily and divided doses, a critical evaluation of benign side effects was precluded by the low mentality of the patients treated. Restlessness in one and anorexia in another patient were reported with doses of 23 and 35 mg. per kilogram, respectively. Drowsiness was increased in 4 patients when Pyrictal was administered in addition to phenobarbital and Dilantin and persisted in 1 patient; 9 patients were said to be more alert and active, and 2 were less irritable. Postictal depression was relieved in 3 patients whose major seizures recurred. In some patients, daily doses of 30 and 40 mg. per kilogram were given continuously without occurrence of side effects.

DISCUSSION

The inefficacy of present methods of treatment of febrile seizures observed in a previous clinical study has been confirmed by laboratory tests in animals. Aspirin, phenobarbital, and Dilantin are the therapeutic agents commonly employed. The inadequacy of aspirin may be explained in part by the failure of its antipyretic effect in the presence of a rising temperature. While loss of heat in a febrile patient is augmented by aspirin, heat production is not inhibited; the optimum antipyretic effect is obtained when the administration of the drug coincides with the expected defervescence[9] and after the risk of occurrence of a febrile seizure has passed.

Febrile seizures in children and those induced in animals are principally clonic in type.[10] They resemble Metrazol seizures in

pattern and in their response to anticonvulsant drugs. Dilantin is ineffective against Metrazol and exacerbates fever-induced seizures in animals. In children with febrile seizures uncomplicated by spontaneous seizures, long-continued administration of Dilantin is unwarranted. Phenobarbital is effective in the control of fever-induced seizures in animals, but the protective index or margin of safety is less than one. That large and toxic doses of phenobarbital would be required for the prevention of febrile seizures is suggested by the results of both laboratory and clinical studies. In a controlled evaluation of conventional methods of treatment, the prophylactic value of continuous administration of phenobarbital, in doses adequate for the prevention of nonfebrile seizures, was not superior to that of intermittent therapy alone. Seizure control was poor and of questionable degree in the patients of both groups.[4] The protective indices of Gemonil, Tridione, and Miltown, determined in animal studies, were relatively low, and the potential value of these drugs in the treatment of febrile seizures is limited by their toxicities.

Of various chemicals screened for antifebrile-anticonvulsant activity in animals, Pyrictal proved the most potent agent; its protective index was greater than one and relatively high when compared with phenobarbital and other conventional anticonvulsants. The properties of Pyrictal observed in laboratory tests approached those of the ideal therapy for febrile seizures as defined above. Anticonvulsant and antipyretic effects were obtained during induction and the rising stage of fever and in response to nontoxic doses. Sedation was not remarkable, and, indeed, in doses larger than those necessary for prevention of seizures in animals, signs of central nervous system excitation were observed. Its action was relatively rapid on oral administration, and, apart from patients with the complication of nonfebrile seizures who require continuous anticonvulsant medication, the intermittent administration of Pyrictal at onset of acute infection appeared adequate. On the basis of laboratory tests and preliminary clinical trials, the new compound appears superior to agents commonly employed for the prevention of febrile seizures. More prolonged and further controlled studies of its clinical efficacy seem warranted.

The action of anticonvulsant and antipyretic drugs in the prophylactic therapy of febrile seizures should be augmented by tepid baths and other simple measures for the facilitation of loss of body heat. Antibiotics, essential in the treatment of an associated acute bacterial infection, may possibly tend to exacerbate the febrile seizure, and unnecessarily large doses should be avoided in young infants. The suggestion by Lennox[1] that certain antibiotics might conceivably heighten the convulsive tendency is supported by the present study.

Factors in addition to fever may be important in the etiology of febrile seizures. Alterations in the balance of water and electrolytes and immune reactions to the toxic products of infecting organisms may require correction. Rapid hydration with hypotonic fluids is contraindicated,[11] and adrenocorticoids and antihistaminics, sometimes advocated for the prevention of the injurious effects of infection on cell membranes,[12] should be employed with caution and only in hyperpyrexia and status epilepticus, which resist conventional therapies.

SUMMARY

The effects of various classes of pharmacologic agents on febrile seizures have been studied in animals and the inadequacy of conventional therapies has been confirmed. A method has been introduced for the laboratory evaluation of drugs with potential activity against febrile seizures.

Pyrictal, a new therapy, has been developed for the prophylaxis of febrile seizures. In laboratory tests, it appears superior to drugs in current use. Compared with phenobarbital, it is equally potent as an anticonvulsant, and has minimal sedative effects and only one third the toxicity; an antipyretic effect is obtained with nontoxic doses. In clinical trials, Pyrictal has had antipyretic activity in children with fever and acute infection, anticonvulsant effects in institutionalized epileptic patients, and antifebrile-anticonvulsant properties, which appear superior to those of phenobarbital, in children with fever and previous histories of febrile seizures. In epileptic patients, Pyrictal appears to be most effective in the treatment

of major clonic, opisthotonic, and minor absence seizure patterns; major tonic seizures are not well controlled.

The authors are indebted to Dr. Richard C. Cooke for permission to conduct the clinical trial of Pyrictal in nonfebrile epileptic patients at the Myles Standish State School, Taunton, Mass., and to Dr. Philip R. Dodge of the Neurology Department, Massachusetts General Hospital, Boston, for his encouragement. Laboratory studies were aided by a grant from Burroughs Wellcome & Co. (U.S.A.) Inc.

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FOSTER ELTING BENNETT

Foster Elting Bennett, a junior member of the American Academy of Neurology, died in Philadelphia on February 22, 1960, following a brief illness. He had just completed his neurologic residency at the Philadelphia General Hospital on December 31, 1959.

He was the son of Dr. A. E. Bennett of Berkeley, Calif.

A graduate of Dartmouth College and Johns Hopkins University, he interned at the Philadelphia General Hospital and obtained his neurological training at the Illinois Neuropsychiatric Institute and the Philadelphia General Hospital. His residency was interruped by military service.

CASE REPORT

Hyperosmolarity associated with a hypothalamic lesion

Elliot D. Weitzman, M.D., and M. Howard Triedman, M.D.

DURING THE PAST seventy-five years, there has been considerable interest in the role of the central nervous system in the control of sodium and chloride metabolism. Claude Bernard[1] noted in 1858 that a lesion in the floor of the fourth ventricle produced a chloride diuresis in animals. Since that time, both animal studies[2,3] and reports of clinical cases have suggested a direct relationship between damage to areas of the brain and to both salt-retaining[6–13] and salt-losing syndromes.[4,5] More recently, a number of authors[5,7,14,18] have doubted that the phenomena of hypernatremia and hyperchloremia associated with intracranial disease are primary neurogenic effects. They conclude that the observed hyperosmolarity is related to unrecognized water deprivation, secondary to impaired water intake and/or excessive water loss.

We are, therefore, presenting a case of central nervous system disease associated with hypernatremia and hyperchloremia in which the factors related to water deprivation have been studied.

CASE REPORT

J.S., a 27-year-old white female, was admitted to the Neurological Institute of New York on April 28, 1958, with symptoms of confusion and hypersomnolence of several months' duration. The patient was in good health before the birth of her last child one year before admission. There was no spontaneous recurrence of menses after delivery. Hormonal therapy, however, was related to one episode of vaginal bleeding. Five months before admission, the patient had an episode of frequency and dysuria, of one to two weeks' duration, which was treated by her family physician as a bladder infection. A weight gain of 20 to 25 lb. occurred postpartum without obvious change in dietary pattern. However, in the five months before admission, she lost 15 lb. During this period, she was noted to be episodically confused and appeared withdrawn; her speech was often inappropriate, although at times her thinking was clear. Emotional lability became apparent as well. Hypersomnolence was noted, with alteration of the normal sleep cycle. A progressive increase in the severity of these symptoms occurred, and, by two weeks before admission, she was unable to do routine housework, would frequently sleep twenty-four hours at a time, and was disoriented for persons, places, and time. During this two-week period, she complained of severe intermittent bifrontal headaches. No symptoms of visual disturbance, diplopia, excessive thirst, nausea or vomiting, seizures, or motor dysfunction could be elicited. There was no history of trauma. Changes in the retinal papillae were noted by a consulting physician, and the patient was referred to the Neurological Institute.

On admission, the blood pressure was 98/68, the pulse 104 and regular, temperature 100° F., and respirations 20 per minute. The patient was a well-developed, well-nourished, somnolent white female, weighing 106 lb., who did

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TABLE 1

Date	*Hospital day*	*Intake*	*Output*	*Specific gravity*	*Body weight*	*Na*	*Cl*	*K*	CO_2	*Blood urea nitrogen*	*Hemoglobin*	*Hematocrit*
April 28, 1958	1				105							
	2	1,300	680	1.014		150.7	126.4	3.9	25.8	14	14.8	
	3	2,100	1,350									
May 1	4	2,500	1,885	1.002							15.2	44%
	5	4,695	2,000			164	130.6	3.7	26.9		14.6	45%
	6	3,150	1,400									
	7	4,125	2,575									
May 5	8	3,390	3,260									
	9	2,050	2,500									
	10	3,080	1,125									
	11	2,536				152.4	112.3	3.7	27.9			
	12											
May 10	13	3,165	2,550									
	14	2,690	2,575	1.008								
	15	3,075	2,245			162						
	16	2,680	2,175									
	17	1,610	1,160	1.012		158.8	124	3.8	27.3		13.2	36%
May 15	18	1,015	1,240	1.012	129.5					16		
	19	3,855	1,646	1.002		158, 144.9	130, 109.7		25.9			35%
	20	5,775	1,413	1.016	130	149.2	123.2					34, 36%
	21	2,200	1,528	1.006	130	137	108.2					41%
	22	2,340	1,210	1.008	125	151.6	123.1	3.9	16.5	32		36%
May 20	23	3,735	1,710	1.006	128	145.3			17.1	26		
	24	3,330	920		130	140,134.5, 145.2						
	25	1,245	1,500		134.5	133.8		3.1		21		
	26	1,225	2,550	1.012	129	152.6	123	3.4				
	27	2,200	1,910	1.004	128				16.8			26%
May 25	28	2,280	1,860		125.5							
	29	2,100	1,360		125	170		4.5				29%
	30	1,950	1,285	1.014	124.5							
	31	2,900	1,170	1.016		165		3.4				
	32	2,530	1,640			161	131.3	4.1	24.7			
	33	2,310	1,100									
May 31	34	2,800	1,520			162		3.93				30%
June 1	35	2,000	1,640									
	36	2,875	1,110		125	152.1	118.9	3.4	25.3			
	37	3,000	2,940		126	154.6	114	3.8	25.7			
	38	3,160	1,290		125.5	155	123.6	4		22,25		31%
June 5	39	3,000	1,150		128.5	150.8	117.6	3.7	25.4	23		31%
	40	4,350	680		130							28%
	41	1,150	605		137	132	97.2	4.31				
	42	1,680	425		137	128	108					
	43				137	126.8	97.2	4.4	22.1			
June 10	44	3,135	5,330			137.6	106.2					
	45	2,200	3,648	1.003		159			24.6			34%
	46	1,445		1.010		178	138	3.9	19.5	13		33%

TABLE 2
CEREBROSPINAL FLUID VALUES

Date:	*April 30*	*May 6*	*May 7*	*May 14*	*May 19*	*May 23*	*June 11*
Sugar, mg. per cent	67	35	44	34	44	68.8	63
Protein, mg. per cent	Ventric = 70	210	194	249	185	165	152
Protein, mg. per cent	Lumbar = 263						
Gamma globulin, per cent						30%	
Red blood count	12,500	8,750	11,500	6,250	12		
White blood count	3	395	235	117	114	57	24
Polymorphocytes, per cent		80%	78%	30%	10%	59%	
Lymphocytes, per cent		20%	22%	70%	90%	41%	

not appear acutely or chronically ill. She was easily roused and was able to follow simple commands but would lapse into sleep during the examination. The patient was disoriented for time. She knew that she had been hospitalized but thought it related to an automobile accident. She was apathetic, confused, seemed out of contact, and related appropriately only briefly. Her skin was dry, and yellow patchy scales were present on her knees and ankles. The remainder of the general examination was within normal limits.

Cranial nerve examination revealed indistinctness of the nasal portion of the disk margins and a suggestive left lower facial weakness; the remainder of the cranial nerves were normal. No signs of meningeal irritation were found. Her gait was shuffling and unsteady and thought to be compatible with her drowsy, apathetic mental state. No specific motor defect was noted. Equilibratory and nonequilibratory coordinative functions were normal, as were strength and sensation. Reflexes were equal and active. The Babinski toe sign was equivocally present on the left.

The presumptive diagnosis on admission was brain tumor, possibly in the right frontal lobe. Laboratory studies were done on admission and revealed a urinary specific gravity of 1.014; hemoglobin, 14.8 gm. per cent; red blood count, 4,450,000; erythrocyte sedimentation rate, 38 mm. per hour; fasting blood sugar, 91 mg. per cent; blood urea nitrogen, 14 mg. per cent; sodium, 150; chloride, 126.4; potassium, 3.9; and carbon dioxide content, 25.8 mEq. per liter. An electroencephalogram was diffusely and moderately abnormal, without focal signs.

On the day after admission, a right common carotid arteriogram was performed. The only abnormality noted was widening of the loop of the anterior cerebral artery, suggesting ventricular dilation. A recumbent anteroposterior chest roentgenogram revealed diffuse infiltration throughout both lung fields. On the third hospital day, a ventriculogram revealed "failure of filling of the anterior portion of the third ventricle with suggestion of a mass lesion in the region of the cisterna interpeduncularis." Surgical exploration of the base of the brain through a right temporal craniotomy revealed no evidence of extrinsic tumor in or around the sella turcica.

The immediate postoperative course was uneventful, but laboratory studies revealed the following findings (Table 1): [1] serum sodium and chloride were persistently elevated; [2] serum potassium and carbon dioxide were normal; and [3] no significant azotemia was present. The patient was receiving adequate fluids (Table 1, days 5 through 16), and no clinical evidence of dehydration was noted. Urinary output was not markedly increased. Repeated cerebrospinal fluid examinations during the six-week period after operation persistently revealed pleocytosis, low sugar, and elevated protein with an elevated gamma globulin fraction (Table 2).

Because of persistence of the hyperosmolar state, the patient was transferred to the Metabolic Service of Presbyterian Hospital for evaluation on the seventeenth day after admission. Examination at this time revealed somnolence, nuchal rigidity, and dry skin, with greasy deposits on the extensor surfaces of elbows and knees. During the twenty-five days spent on

the metabolic ward, the patient's neurologic findings remained essentially unchanged. However, the course was complicated by an acute flare-up of chronic urinary tract infection on the twentieth hospital day. During its treatment, a sensitivity reaction to Furadantin, with skin rash and eosinophilia, occurred. In addition, on the twenty-eighth hospital day, a deep thrombophlebitis of the left leg developed.

On the nineteenth hospital day, a Hickey-Hare test was attempted. After eight hours of water deprivation, 2,150 cc. of distilled water was given by mouth in a ninety-minute period. Urinary flow did not exceed 1 cc. per minute for twelve hours after this water load. During the test, isoosmolarity was obtained. The sodium fell from 158 to 144 mEq. per liter and the chloride from 130 to 109 (Table 1) without change in the patient's clinical state. The total fluid intake that day was 3,855 cc., and the total output was 1,646 cc. A repeat of this attempt at water loading on the twentieth day confirmed the findings of the previous study. Although 1,700 cc. of water was given by nasogastric tube during a three-hour period, the urinary volume did not exceed 1.6 cc. per minute in this period. The patient did not diurese in response to an acute water load. No change in the hematocrit volume was observed.

On the twenty-fourth and twenty-fifth hospital days, a study of the total exchangeable body sodium was done.[15,16] For two days before this study and during the forty-eight hours of urine collection, the total sodium intake was 67 mEq. and the total potassium intake was 41 mEq. per day. The administered radioactive sodium was distributed in 20.3% of the body weight in three hours, 26.6% in twenty-four hours, and 25.6% in forty-eight hours. The serum sodium was 140 mEq. per liter at three hours, 134.8 at twenty-four hours, and 145.2 at forty-eight hours. The total twenty-four-hour urinary output of sodium on the twenty-fourth day was 3.1 mEq. with a total output of 3,330 cc. and, on the twenty-fifth day, was 2.7 mEq. with a total output of 1,245 cc.

On the thirtieth hospital day, the twenty-four-hour urine volume of 1,285 cc. contained 32 mEq. of sodium. During the seven days before this collection, the patient had received 78 mEq. of sodium per twenty-four hours. The serum sodium on the twenty-ninth day was 170 mEq. per liter and on the thirty-first day was 165. This study suggested that the patient was in positive sodium balance during the test period.

Urinary corticoid excretion was normal; 17-ketosteroid excretion was 5.6 mg. per twenty-four hours, and ketogenic steroid excretion was 16.3 mg.

During a three-day period, the thirty-eighth, thirty-ninth, and fortieth hospital days, water loading was accomplished with intravenous fluids and Pitressin tannate. The patient received 3 daily intramuscular injections of 5 units of aqueous Pitressin tannate. Total fluid intake during this period was 10,510 cc., and the urinary output totaled 3,120 cc. The patient gained 12 lb. The serum sodium fell from 155 to 132 mEq. per liter and serum chloride from 123.6 to 97.2 mEq. per liter. On the third day, the patient was noted to be less responsive than usual, her face was pale and puffy, the body temperature fell from normal values to 94° F., and Cheyne-Stokes respiration developed. The patient appeared to be water-intoxicated. Water loading was discontinued, and gradually, over a two-day period, the patient's sensorium improved and the temperature returned to normal. Four days after termination of water loading, diuresis occurred (Table 1) with a progressive elevation of both serum sodium and chloride values.

After completion of the metabolic studies, the patient returned to the Neurological Institute on the forty-second hospital day. Repeat neurologic examination revealed lethargy, disorientation, blurring of the nasal portion of the disk margins, mild right peripheral facial weakness; and suggestive left hemiparesis. Reflexes were equal and active, without Babinski toe signs.

Recrudescence of the urinary tract infection occurred with a high fever and tachypnea. Circulatory failure developed, and in spite of antibiotics, Levophed, intravenous fluids, and compound F, the patient died on the forty-sixth hospital day. Laboratory values on the day of her death were sodium, 178; chloride, 138; potassium, 3.9; carbon dioxide content, 19.5 mEq. per liter; blood urea nitrogen, 13 mg. per cent; serum *p*H, 7.49; specific gravity, 1.010; and hematocrit, 33%.

TABLE 3
ADDITIONAL LABORATORY DATA

Date:	*April 29*	*May 3*	*May 8*	*May 23*	*June 8-10*
Ca, mg. per cent				8.8	
P, mg. per cent				3.3	
Fasting blood sugar, mg. per cent	91			88	
Erythrocyte sedimentation rate, mm. per hour	38				
Serum gamma globulin, mg. per cent			1.2		
Gonadotropins			10 mouse units = 0		
17-ketosteroids, mg. per cent			5.6		
Ketogenic steroids, mg. per cent			16.3		
Old tuberculin 1:1,000					Negative
Old tuberculin 1:100					Negative
Electrocardiogram	Flat T waves				

PATHOLOGY

The pleural surfaces of the lungs had multiple subpleural bullae. On section of the lung, multiple thin-walled cystic spaces 8 to 10 mm. in diameter were found. On microscopic examination, these proved to be scattered areas of fibrosis with occasional nodule formation surrounding the cysts. Large mononuclear cells and eosinophils were found in the fibrotic areas. The liver showed similar lesions in the portal triads. An organizing thrombosis was found in the right common iliac vein and inferior vena cava. Both gross and microscopic evidence of cystitis and pyelitis was seen. A moderate amount of milky fluid exuded from the breast tissue on gross section. A small nodule was found at the site of injection of Kveim antigen. This proved to be a collection of perivascular histiocytic lymphocytes and a few multinucleated giant cells.

The adrenal glands demonstrated on microscopic section "two areas of haphazard deposition of what resembles collagen." The left kidney held 3 foci of granulomatous formation. No other findings were noted in the general pathologic examination.

NEUROPATHOLOGY

Gross brain. Brain weight was 1,275 gm. An operative defect of 4.5 x 3 cm. was present on the ventral surface of the right temporal lobe. Ventricular needle tracts were present in the cerebral cortex and subcortical white matter. Sections of the brain revealed a well-defined but not sharply demarcated lesion in the hypothalamus, involving the tuber cinereum, dorsal portion of the infundibulum, and region between the optic tracts. The lesion was gray, with islands of more opaque grayish-white material interspersed. The total anteroposterior extent of the lesion was approximately 1 cm. and the greatest dorsoventral and transverse diameter was 1.5 cm. No other gross abnormalities of the parenchyma were seen.

Microscopic. Examination of the hypothalamic region revealed a granulomatous lesion, which was fibrotic and contained large mononuclear cells, lymphocytes, and eosinophils. Large numbers of blood vessels were present, as well as fine, compact connective tissue trabeculae. The lesion extended dorsally into the ventral extremities of the pillars of the fornices and reached the wall of the optic recess on each side. It extended laterally into the anterior gray of the hypothalamus, as well as into the medial portion of each supraoptic nucleus. It extended posteriorly to the level of the corpora mammillaria. An extensive search revealed no other granulomatous lesions.

The final pathologic diagnosis arrived at by the Departments of General Pathology and Neuropathology was that the patient had systemic, nonlipid histocytosis (Figs. 1 and 2).

DISCUSSION

A case has been presented of a 27-year-old white female with a history of twelve months' duration of amenorrhea, hypersomnolence, and disorientation, in which a state of hyperosmo-

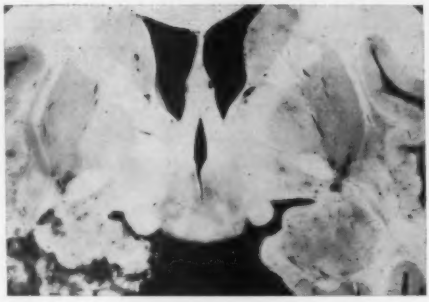

Fig. 1. Coronal section through midhypothalamus, demonstrating extent of lesion

Fig. 2. Low power magnification of stained granulomatous lesion

larity was a persistent finding during hospitalization. The clinical course of the disease was one of progressive debilitation associated with recurrent urinary tract infection and thrombophlebitis. Anatomopathologic study revealed a hypothalamic lesion, granulomatous in nature and suggestive of nonlipid histiocytosis. No other lesions of the central nervous system were found. Similar granulomatous lesions were noted in other organs. Studies were done to delineate the cause of this patient's hyperosmolar state.

The persistence of normal values of hematocrit, potassium, carbon dioxide, and blood urea nitrogen in association with elevated serum sodium and chloride suggests that the observed hyperosmolarity was not solely the result of water deprivation and reduced intravascular volume. Renal blood flow was sufficient to maintain normal blood urea concentration. Extracellular fluid volume, as determined by the exchangeable body sodium study, also was within normal limits.

Excessive water loss from a solute diuresis was not present. Azotemia, hyperglycemia, and/or glycosuria were not noted during the period of hospitalization.

The classic signs of diabetes insipidus were not present. Urine volume was not excessive, and the patient, when alert and communicative, did not have excessive thirst. She was able to concentrate urine to values above 1.010, but the urinary specific gravity was usually rather low. The kidneys were unable to respond to an acute water load by prompt diuresis.

Hyperosmolarity on the basis of hyperadrenalism is also unlikely. Both urinary 17-ketosteroids and ketogenic steroid values were within normal limits. The absence of hypertension, edema, and potassium-wasting suggests that primary aldosteronism was not present.

Known causes of hypernatremia and hyperchloremia did not appear to contribute to the patient's hyperosmolar state. Water deprivation, of either renal or extrarenal origin, was not present. The suggestion is therefore made that the hyperosmolarity was related to the hypothalamic lesion noted on pathologic examination.

Allott[6] was the first to note a relationship between hypernatremia and central nervous system disease. A number of clinical reports since have attempted to demonstrate an etiologic relationship between central nervous system lesions and hyperosmolarity. Most notable among these have been the series of case reports by Peters,[7] Sweet and associates,[8] Cooper and MacCarty,[9] Higgins and associates,[10] Engstrom and Liebman,[11] Schoolman, Dubin, and Hoffman,[12] Allott,[13] and Anthonisen, Hilden, and Thomsen.[17] A number of authors[5,7,14,18] have expressed doubt that a specific relationship exists and have ascribed the observed hyperosmolarity to unrecognized dehydration. They have clearly shown that many cases designated as examples of solely neurogenic hypernatremia cannot be so considered in that the known causes of hyperosmolarity, such as urea diuresis, diabetes insipidus, and exogenous dehydration in the co-

matose patient, have not been eliminated. The present case suggests, however, that an additional "neurogenic" factor may have contributed to the hyperosmolarity noted.

The localization of a lesion or lesions responsible for neurogenic hyperosmolarity has not been well delineated in the clinical cases reported. However, a significant number have had lesions in and around the hypothalamus and its frontal lobe connections.[6,8,9,19]

Animal experimentation also suggests a hypothalamic localization. Stevenson, Welt, and Orloff[3] demonstrated hypernatremia in rats associated with a lesion in the ventromedian nucleus of the hypothalamus. Lewy and Gassmann[2] produced significant hyperchloremia after unilateral stimulation and destruction of the paraoptic hypothalamic nuclei in cats. Recently, Keeler[22] reported that lesions in the area of the paraventricular nuclei resulted in a threefold increase in urinary sodium excretion for twenty-four hours after the operation.

In the case presented, the only area of involvement of the central nervous system was the hypothalamus; the pituitary gland was intact. However, since the lesion involved almost all of the hypothalamic structures, discrete nuclear localization was impossible.

The pathways and mechanism whereby the hypothalamus can influence tubular reabsorption of salt are unknown. A specific neural pathway has not been clearly demonstrated, but several authors[20,21] have shown that unilateral denervation of the kidney produces an increase in excretion of both sodium and water without concomitant increase in glomerular filtration, suggesting a possible neural control of tubular salt reabsorption.

SUMMARY

A case has been presented in which hyperosmolarity has been observed in association with a solitary central nervous system lesion located in the hypothalamus. The results of a metabolic study were interpreted as demonstrating that water deprivation, of either renal or extrarenal origin, was not the causative factor for the observed hyperosmolarity. A study was made of the known causes of the hyperosmolar state, and an adequate explanation was not found. Specifically, water deprivation was not considered the causative factor. A brief review of the past clinical and experimental literature was made, and a route of control of renal tubular salt reabsorption under hypothalamic influence was discussed.

A more complete pathologic description of this case will be included in a forthcoming review of granulomatous diseases of the nervous system by the Department of Neuropathology.

The authors wish to thank the staff of the Metabolic Service for the studies performed by them. We are also indebted to Drs. George Seiden, Robert Fishman, and H. Houston Merritt for their suggestions and editorial help.

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Microelectrode studies of unit discharges in the sensorimotor cortex

Investigations in monkeys with experimental tremor

J. Pierre Cordeau, M.D., Jan Gybels, M.D., Herbert Jasper, M.D., and Louis J. Poirier, M.D.

THE PHYSIOPATHOLOGIC mechanism that produces the tremor movements of paralysis agitans is unknown. Some tentative hypotheses have been put forward in the past and were usually based on pathologic findings, electromyographic studies, or results of the various surgical approaches to the treatment of parkinsonism in human patients. But, to date, there is little neurophysiologic data to support these hypotheses.

Until quite recently, one of the main reasons for this paucity of information has been the impossibility to reproduce a lasting parkinsonian type of tremor in experimental animals. Now that this difficulty seems to have been partially overcome, at least in monkeys,[1–6] it can be hoped that physiologic data will rapidly accumulate and provide a foundation on which to base further speculation on the mechanism of tremor or of involuntary movements in general.

The present study was undertaken with this purpose in mind. Mesencephalic lesions were placed in monkeys with the aim of producing a peripheral postural tremor. The characteristics of this tremor were studied clinically and electromyographically so as to compare it to that seen in parkinsonian patients. Finally, microelectrodes were inserted into the brain and records obtained of the firing of neurons from sensory and motor cortical areas while the peripheral tremor was in activity. Microelectrode recordings of subcortical structures are now being made and will be reported separately.

MATERIAL AND METHOD

The experiments were performed on 2 Macaca mulatta monkeys (BG11 and BG14), and all surgery was done under general anesthesia (Nembutal) with full sterile precautions.

In a first operation to produce tremor, the animals were placed in the stereotaxic instrument and a monopolar coagulating electrode was introduced vertically through a small bur hole in the skull. The region aimed at was the ventromedial part of the mesencephalic tegmentum (stereotaxic coordinates: frontal, 6.5 to 7; lateral, 2; horizontal, 0 to −3). Since this region is close to the zone of exit of the third nerve fibers, electrical stimulation at that point usually produced a pupillary constriction as well as upward and inward deviation of the ipsilateral eye. This reaction was used as an indication of the correct placement of the electrode before coagulation. Lesions were placed in the right half of the brain stem only, and, after coagulation, the animals were returned to their cages and kept under observation for the appearance of tremor in the contralateral limbs.

The technic whereby microelectrode recording could be carried out in the unanesthetized chronic preparation over extended periods of time has been described elsewhere.[7] In brief, this technic involved the placing of hollow nylon screws into the skull of the animal under general anesthesia. The location of the screws was determined with the aid of evoked potentials for sensory cortical areas and by electrical

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Dr. Gybels is a fellow of the World Health Organization.

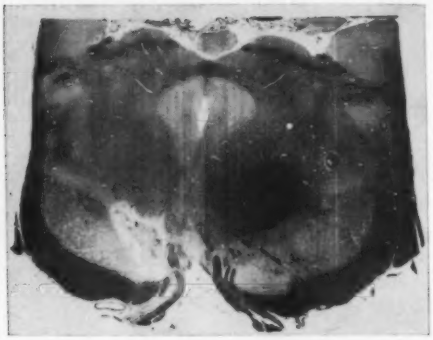

Fig. 1. Photomicrograph of the brain stem of BG11 showing the extent of the lesion in the ventromedial region of the tegmentum. This animal had a postural tremor in both arm and leg of the contralateral side. Weil stain

stimulation for motor areas. After recovery from the anesthesia, the animals were placed in a plastic chair that prevented them from tampering with screws or wires attached to their heads. Two to three days after such an operation, recordings were begun with tungsten microelectrodes mounted in a small microdriver assembly that could be attached to the nylon screws.

The tremor movements were recorded through a Grass force-displacement transducer (Model FT03) to which the limb was attached. Two methods were used for recording the electromyographic activity. In the first, the activity was recorded between a surface electrode (silver disk attached to the limb with collodion) and a monopolar needle electrode inserted into the muscle. At other times, concentric bipolar needle electrodes were used.

The unit activity, the electromyogram, and the tremor movements were displayed simultaneously on a 4-beam cathode ray oscilloscope and photographed with a Grass camera (Model C4). The Grass Model P-6 preamplifier with cathode follower and probe (MEP6) was used for the unit activity, and Tektronics preamplifiers (Model 122) were used for the electromyogram and tremor movements.

After completion of the study, each animal was killed, the brain was fixed in formalin, and the size and position of the mesencephalic lesion were studied in Weil and Klüver and Barrera stained sections.

RESULTS

Anatomic data. The extent of the brain stem lesion in one of our monkeys (BG11) is shown in Figure 1. It is not our intention to discuss the histologic data in detail at this time. These will be reported elsewhere[8] and will be based on a greater series of animals, most of which were never studied electrophysiologically. However, two main points of observation could be mentioned here. The first is that the one-sided brain stem lesion encroached upon, and destroyed in part, 3 main anatomic structures. These could either singly or in combination be involved in the production of the tremor phenomenon. They are [1] the medial part of the substantia nigra, [2] the dorsomedial region of the fibers coursing through the pes pedunculus, and, finally, [3] the ventral fibers of the brachium conjunctivum rostral to the decussation. Secondly, it appears from these preliminary results that, in all monkeys in which the lesion was successful in producing tremor, the magnocellular portion of the substantia nigra contralateral to the tremor had completely degenerated. For example, in BG-11 (Fig. 1), in which the actual coagulation destroyed the medial third only of the substantia nigra, retrograde changes were present throughout this cellular aggregate on the same side and were characterized by the nearly complete absence of cellular bodies at this level as well as in regions rostral and caudal to the lesion. It is too early and the data too few to assess accurately the significance of these observations. As mentioned previously, these will be discussed at length elsewhere.

Clinical data. Clinically, the tremor was present in both animals immediately upon recovery from the anesthesia. It involved the arm and leg contralateral to the lesion and was more marked in the upper limb. In neither animal was it confined to any one portion of each limb but could be seen to shift frequently. For example, in the upper limb, the tremor would move from the forearm muscles, where it produced an alternating flexion and extension at the wrist, to the arm and shoulder girdle muscles, producing alternating movements at the

elbow or shoulder joints. It was regular both in amplitude and frequency and belonged to the category of postural or resting tremor. The tremor disappeared during sleep and with voluntary movements of the limb and seemed to be best displayed at an optimum level of general arousal. With the animal completely relaxed in a quiet environment, it had a tendency to decrease in amplitude and disappear. At such times, a loud noise, a flash of light, or presentation of food would make it reappear. On the other hand, when immobilized in an uncomfortable position for recording purposes or when in pain, the animals would become tense and the tremor episodes less frequent and less marked. The animals could and would stop the tremor temporarily by tightly grasping the bars of their cage or sitting on their hands. This tremor persisted unchanged, except in the case of surgical accidents (see below), and was still present at the time of death, several months after the initial surgery.

No true paralysis or paresis of the corresponding limbs was seen. However, there was some hypokinesia, and, when free to choose, the monkeys would prefer to use their intact limbs to pursue such activities as scratching or eating. But, it was observed repeatedly that the animals could use the affected limbs to perform fine movements and could do so with unimpaired strength.

Hypokinesia and postural tremor were the only signs of parkinsonism observed in our monkeys. Facial mimicry remained quite good, even though it may have been somewhat impaired on the side contralateral to the lesion. Rigidity did not appear to be marked, but this was found difficult to assess in the awake, struggling animal, which automatically resists all attempts at handling.

During the early postoperative period, some other signs of a high brain stem lesion, such as torticollis, forced turning, cerebellar dysmetria, and ataxia, were observed, but these regressed completely in one animal, and only a slight torticollis persisted in the second. Anisocoria, due to a lesion of the lateral fibers of the third nerve on one side, persisted unchanged throughout the period of observation.

Electromyographic data. From the above description, it seemed clear that the tremor observed in our monkeys was identical to that seen in patients with paralysis agitans. However, to obtain objective evidence of this similarity, the following electromyographic studies were done, and most of the characteristics reported for the parkinsonian tremor were found reproduced here. These will be briefly mentioned.

Regularity of rhythm and frequency range. As recorded in the electromyogram, the frequency of the tremor was remarkably constant. In one of our animals under study, it never varied more than from 5 to 5.7 cps, that is, from a period of 175 msec. to one of 200 msec. The variations, when they did occur, had a tendency to be mutually compensatory; a short period was usually followed immediately by a longer one and vice versa, so that the over-all frequency remained relatively constant. This should be compared to the similar frequency of 5 cps usually reported in most parkinsonian patients.[9] In human beings, the frequency is fairly constant in any one patient, even though it may vary from 4 to 8 cps from patient to patient. The similarity of frequencies seen in human parkinsonism and in our experimental tremor, if we assume that the basic mechanism is the same, would probably eliminate such factors as weight or inertia of the limb or its resonant frequency as important contributors to this frequency, since these characteristics are quite different in the two species.

Ratio of period of activity to silent period. The ratio of the period of activity to the silent period was usually low and in the neighborhood of 1 to 2, 1 to 3, or less. As reported by Isch,[9] this characteristic, as well as the fluctuations in frequency, were used by Japanese authors to distinguish parkinsonian tremor from intentional and psychogenic or emotional tremor. In the latter cases, the ratio of activity over silent periods is usually fairly high, while the fluctuations in frequency are much greater than in the present type of tremor. However, this low ratio was not always the case; it would increase considerably in the transition periods when the muscle went into tonic or phasic contractions.

Doubling of frequency. For short periods of time, the electromyogram occasionally showed a doubling of the frequency of the tremor rhythm, which became 10 cps instead of 5 cps.

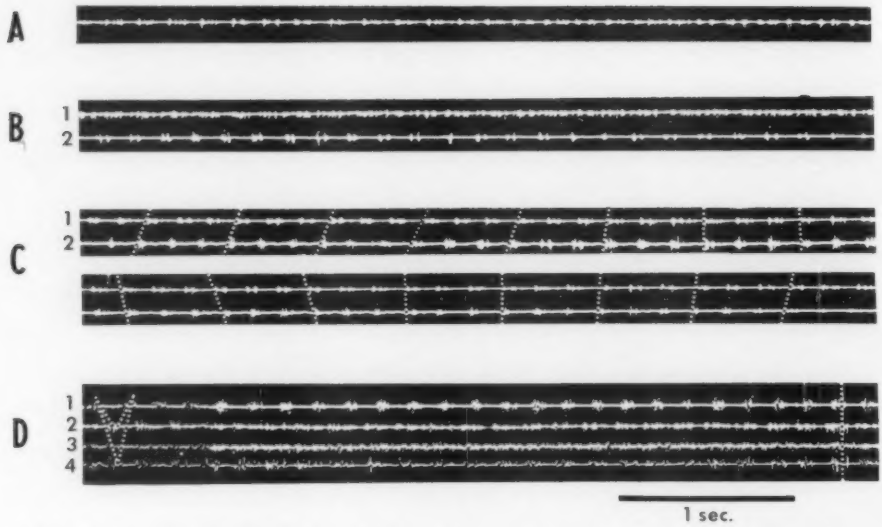

Fig. 2. Electromyographic records of BG14 using concentric bipolar needle electrodes. Record A is from the flexor group of muscles in the forearm of the affected limb and shows a doubling of the frequency of the tremor toward the end of the record. Record B, also from the forearm, shows that the tremor activity in agonists may be accompanied by continuous, tonic activity in the antagonists. Line 1: flexors; line 2: extensors of the forearm. Note the splitting in two of the period of activity in line 2. Record C: the 2 strips are continuous and show the shift in phase between the leg and arm tremor rhythms, first in one direction, then in the other. Line 1: flexors of the forearm; line 2; tibialis anterior. Record D shows that these phase shifts may occur between 2 segments of the same limb (lines 1 and 4) or between agonists and antagonists (lines 1 and 2). Line 1: flexor group of the forearm; line 2: extensor group; line 3: deltoid muscle; line 4: biceps

This is shown in Figure 2A, which is a record obtained from the flexor group of muscles in the forearm. This phenomenon was reported in human parkinsonian patients by Bishop, Clare, and Price.[10] Its significance as far as the central mechanism of tremor is concerned is unknown.

Splitting in two of the period of activity. Another phenomenon, which appears to be different from the preceding one, is the splitting in two of the period of activity, as shown in Figure 2B. Here, the muscular activity is interrupted after some 20 msec. by a silent period, which lasts another 20 msec., and then the period of activity is resumed. It has been thought that this might correspond to the silent period seen in clonus, in which the Golgi tendon organs, excited by the initial contraction, inhibit the motoneurons for a short period of time. The time lapse involved appears to be consistent with this hypothesis. However, this phenomenon is only seen when the tremor activity is of rather low intensity, and it is doubtful if the Golgi tendon organs are brought into play with such a low grade contraction.

Instability of tremor activity. Another visual observation that is given objective form in the electromyogram is the continuous shifting of the tremor activity from one muscle to the next. It was very seldom that the rhythmic activity remained stable and of the same amplitude in any one muscle for more than a few seconds at a time. More frequently, it was seen to be constantly waxing and waning and changing from one muscle to the next, disappearing in one and appearing in another.

The significance of this phenomenon should be kept in mind as far as our attempts to

correlate cortical unit firing with tremor activity as recorded by the transducer is concerned. If, in our microelectrode explorations, we are searching for cells the firing of which is at the origin of the tremor, we cannot expect the synchrony between unit firing and the transducer record to last longer than the tremor activity in any one muscle. It would appear safe to assume that, in line with the continuous waxing and waning of the muscular activity, the firing of the neuron responsible for the tremorgenic impulses will also be short lived. This was usually found to be the case.

Reciprocal innervation. While recording from agonists and antagonists in any one limb, the tremor activity was usually found to be 180° out of phase in the two groups of muscles (Fig. 2D, beginning of lines 1 and 2). However, this was not a constant finding. As in paralysis agitans,[9,11] tremor activity in one group of muscles may accompany continuous tonic activity in the antagonists (Fig. 2B) or the tremor rhythm may be synchronous in agonists and antagonists (Fig. 2D, end of lines 1 and 2).

Phase shifting. While recording simultaneously from muscles in the arm and leg, it was generally found that the two rhythms were locked together in their phase relationship. However, at times there occurred a phase shift between the two limbs. An example of such a shift is shown in Figure 2C, in which line 1 is a record from the flexor muscles of the forearm and line 2 from the tibialis anterior on the same side. Throughout this record, the frequency of the leg tremor remained relatively constant at 5.5 cps. At the beginning of the record, the two limbs were locked in phase, but, soon, the frequency in the arm became 5.7 cps and a gradual phase shift occurred, as shown by the dotted lines. Half way through the record, the tremor in the arm slowed down to a rate slightly less than 5.5 cps and a shift reversal occurred. At the end of the record, the two limbs had returned to their original phase relationship.

This shift in phase of the tremor activity can also be seen between different segments of the same limb such as arm and forearm or even between muscles of the same segment belonging to agonist and antagonist groups (Fig. 2D). The latter shift, which seems to be much less frequent, results in the synchronous firing of agonists and antagonists reported in the previous section.

Since the phase shifts between arm and leg are not constantly present and sometimes occur in opposite directions, such factors as weight or inertia of the limb as well as the length of the proprioceptive reflex arc can probably be discounted as important contributors to the phenomenon; these characteristics remain constant in both limbs. Jung,[11] reporting this phenomenon in human beings, has used it to argue that there is more than one central pacemaker. He is undoubtedly right if by pacemaker he means an anatomic locus such as the respiration center, in which all cells at all times fire in synchrony. However, the fact that the rhythms of arm and leg are most often locked in phase shows that the cells of this pacemaker can and do beat in synchrony. But the shifts in phase occurring between the two limbs, two segments of the same limb, or, again, two muscle groups of the same segment also show that this interlocking of unit activity is not an absolute one and, at such times, there may be as many "pacemakers" as there are muscles involved in the tremor. In other words, the neuronal network with activity responsible for the tremor is probably organized on a somatotopic basis, each part being capable of firing at an independent rate on occasions but the whole usually beating in synchrony.

Microelectrode data. Microelectrode recordings were obtained from the motor and sensory cortex contralateral to the tremor in both arm and leg areas and in the ipsilateral motor cortex, arm area only. Several patterns of unit activity were found to be associated with phasic or tremor movements in the limbs. These were classified into 5 main categories, each pattern being represented in all cortical areas recorded from but in varying degree. Figures 3 and 4 show samples of such unit activity, while Figure 5 is the per cent representation of each pattern in the different cortical areas. These patterns of firing could be described briefly as follows.

No relationship to tremor or phasic movement. In this first category, the unit activity showed no relationship with either tremor or phasic movements of the limbs. In other words, the apparently random firing of the cell

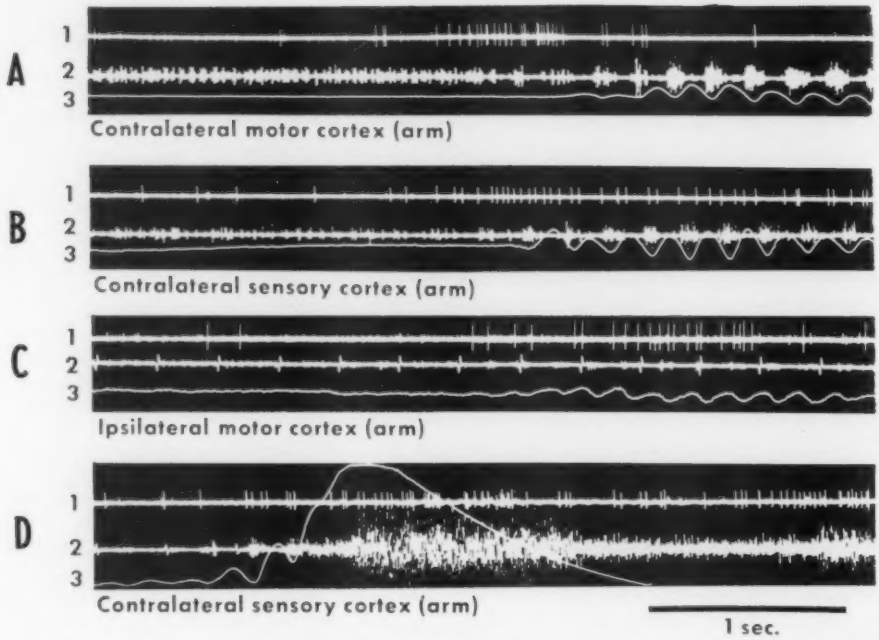

Fig. 3. Sample records of unit activity. In A, B, and C, the units increased their firing rates at the outset of a tremor episode; in D, the firing increased with a phasic movement of the limb. In each record, line 1 is the microelectrode record of the unit activity in the area shown; line 2 is the electromyogram of the deltoid muscle; and line 3 shows the movements of the arm as recorded through a force-displacement transducer. The regular artifacts in line 2 of record C are the electrocardiogram.

went on unchanged during the initiation and pursuance of a tremor episode or of a phasic movement of the limb. As shown in Figure 5, this independent unit firing was the most frequently encountered pattern in the contralateral sensory and ipsilateral motor areas.

Increased firing rate with phasic movements. In the second type of firing observed, the unit activity increased its frequency rate with phasic movements of the limb (Fig. 3D). This pattern was more frequent in the motor areas, both contralateral and ipsilateral, than in the contralateral sensory area (Fig. 5). This even distribution in the motor cortices of both hemispheres is readily understood if it is remembered that these phasic movements were usually the outcome of the animal's struggling against its bonds. In these circumstances, the movements were not limited to the limb attached to the transducer but were usually bilateral and simultaneous on both sides of the body.

In quite a few instances, the phasic movement as recorded by the transducer was either preceded or followed immediately by a few tremor periods (Fig. 3D). At such times, it was quite impossible to tell whether the increase in firing was related to the phasic movement or the tremor episode itself, as in the following category.

Increased firing rate with increased tremor. In this third category were grouped the units with increased firing at the initiation of a tremor episode (Fig. 3A, B, and C). This increase in firing sometimes preceded and sometimes followed the beginning of the tremor; since the same unit very often behaved differently for separate tremor episodes, it was

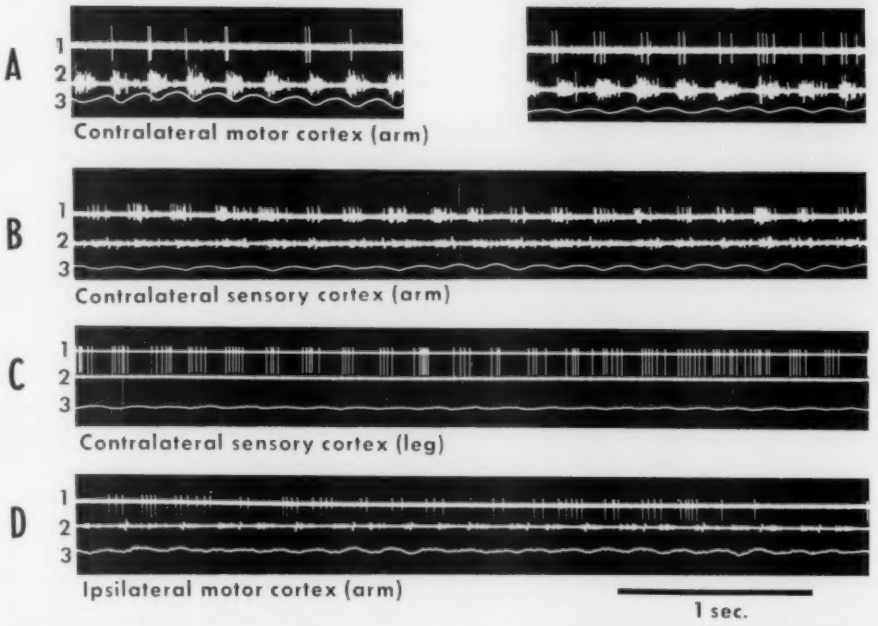

Fig. 4. Sample records of unit activity. In each strip, line 1 is the microelectrode record of unit activity in the area shown; line 2 is the electromyogram of the deltoid muscle in A, B, and D and of the gastrocnemius in C; and line 3 shows the tremor movements of the limb under study as recorded through a force-displacement transducer. In each of these records, the unit is firing, either singly or in bursts, at the frequency and in phase with the tremor movements. Unit D, where this synchrony is not immediately apparent, has been analyzed as outlined in the text, and the resulting histogram is shown in Figure 6. The 2 strips of record A are of the same unit for 2 separate tremor episodes.

impossible to classify these more accurately. This increase in firing with tremor appears to be equally represented in all cortical areas recorded from (Fig. 5).

Unit discharge grouped in synchrony with tremor. The fourth group of cells includes the units that fired in synchrony and in phase with the tremor movements. Figure 4 shows some samples of this pattern of firing for different cortical areas. In records A, B, and C, the synchrony is readily apparent and needs no confirmation other than visual inspection. However, in record D, it may not be self-evident that the cortical unit is firing in phase with the tremorogram of the transducer record. In such doubtful cases, the film records were subjected to the following type of analysis. The films were projected on a screen and amplified, and

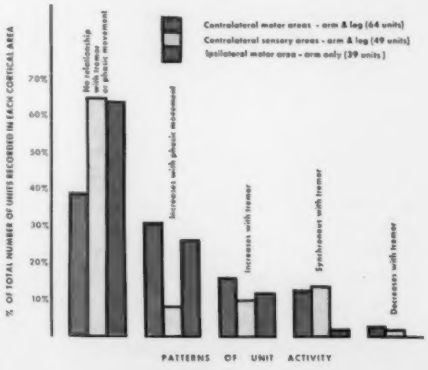
% OF TOTAL NUMBER OF UNITS RECORDED IN EACH CORTICAL AREA
70%
60%
50%
40%
30%
20%
10%
No relationship with tremor or phasic movement
Increases with phasic movement
Increases with tremor
Synchronous with tremor
Decreases with tremor
Contralateral motor areas - arm & leg (64 units)
Contralateral sensory areas - arm & leg (49 units)
Ipsilateral motor area - arm only (39 units)
PATTERNS OF UNIT ACTIVITY

Fig. 5. Distribution of the different patterns of unit activity in each cortical area

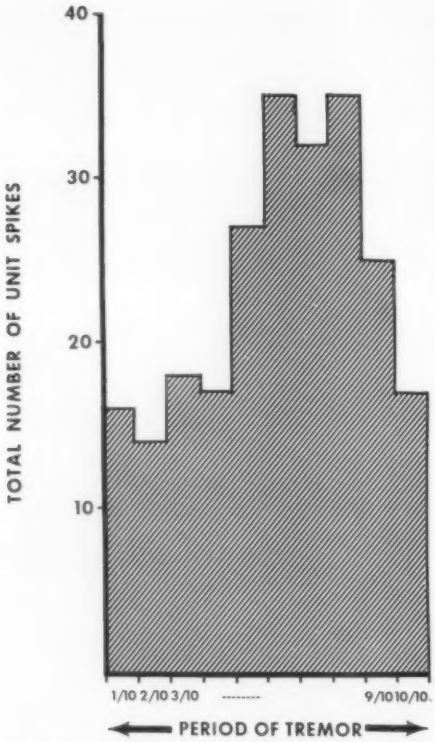

Fig. 6. Histogram of the unit in Figure 4D obtained by adding the number of unit spikes in each tenth of the tremor cycle for 65 consecutive periods of tremor. The graph shows that this unit fires from 2 to 3 times more frequently during the second half of the tremor period than at other times. The χ^2 test shows this preferential firing to be significant at the 99% level.

each tremor *period* was divided into 10 equal parts. The number of spikes in each tenth was then noted and summated over several successive tremor cycles. Figure 6 is a graphic representation of the data obtained in this way for unit D of Figure 4, for 65 consecutive tremor movements. This histogram shows that the unit fired some 2 to 3 times more frequently during the second half of the period of tremor than at other times. Use of the χ^2 test showed this preferential firing to be significant at the 99% level. All units reported here as firing in synchrony with the tremor were found to be at this minimum significance level. Approximately 14% of the units recorded from the contralateral motor and sensory areas were firing in synchrony and in phase with the tremor. A much smaller percentage was obtained from the ipsilateral motor area (Fig. 5).

It probably should be stressed that these data provide minimum figures for cells beating at the same frequency as the tremor. These are units in which the relationship is certain. Since it is notably difficult or impossible to record from the same unit for any length of time in the chronic, awake animal and since each muscle is only sporadically involved in the tremor activity, as discussed previously, it becomes a matter of chance that the unit will fire at the frequency of the tremor while it is being recorded. It is probably safe to assume that, with perfect recording technics completely under our control, a larger number of cells would be found to beat at the tremor frequency.

Decreased firing rate with increase in tremor. Finally, the last pattern of activity seen was that of cells which either decreased or completely stopped firing at the beginning of a tremor episode, only to resume firing later in the record. These were very few (Fig. 5).

To summarize briefly, it appears that:

1] At least 11 to 14% of the cells sampled by our microelectrode technic in the contralateral sensorimotor cortex fire in synchrony and in phase with the tremor.

2] From 10 to 16% of cells increased their rates of firing either just before or immediately after initiation of a tremor episode, but these were evenly distributed in areas sampled.

3] About 25 to 30% of cells from the contralateral and ipsilateral motor areas increase their firing rate with a phasic movement of the limb. A somewhat lower percentage (8%) did so in the contralateral sensory area.

4] The firing pattern was not altered during tremor in about one third of units sampled in the contralateral motor area and in about two thirds of those in the contralateral sensory area for a given limb.

DISCUSSION

From the clinical and electromyographic data reported, it would appear that the experi-

mental tremor under study is very similar and closely related to that seen in patients with paralysis agitans. The similarity between the two phenomena extends to the pathologic findings in the brain stem of the two species. As in our monkeys, the most frequently reported finding in human parkinsonism is a degeneration of the neurons of the substantia nigra.[12]

As far as the microelectrode data are concerned, these are preliminary results only and no definite conclusion can be reached at this time as to the significance of the different patterns of unit activity observed. However, one fact emerges quite clearly: the direct involvement of the contralateral sensorimotor cortex in the tremor movements. Of the units recorded from in this cortical area, approximately 14% fire either singly or in bursts of spikes, at the same frequency and in synchrony with the tremor. Another 11 to 15% increase their rates of firing either just before or immediately after onset of the tremor as recorded at the periphery. A somewhat larger group of cells (31% from the motor cortex and 8% from the sensory cortex) increase their rates of firing when the animal performs a movement with its contralateral limb. These phasic changes in the position of the limb were quite often accompanied or followed immediately by tremor movements, but, in these circumstances, it was impossible to attribute with certainty the increase in firing to either the phasic movement or the tremor itself. All these findings would seem to speak in favor of a significant participation of the sensorimotor cortex in the production of tremor.

The following incidental finding of this research strongly supports this view. As the nylon screws were being placed in the skull overlying the arm or leg motor areas, they were sometimes screwed in a little too deeply and compressed the underlying cortex. After recovery from the general anesthetic, it was noted that, in these instances, the tremor had disappeared from the limb corresponding to the area compressed, while still present and vigorous in the other limb. At times, but not always, disappearance of the tremor was accompanied by a clinically observable paresis in the same limb. The usual procedure in these circumstances was to unscrew the nylon plug slightly in order to free the underlying cortex. This was normally followed, after a few hours or a few days, by the gradual reappearance of the tremor, which often resumed its former state. There is no doubt that this points to the necessity of an intact and functional motor cortex for tremor to be present in the corresponding limb. Whether the role of this cortical area is that of a true pacemaker for tremorogenic impulses or confined to an "energizing" action that raises the excitability of the anterior horn cells sufficiently for the tremor to appear is still an open question.

The importance of a functional motor cortex and intact pyramidal tract for tremor to be present in parkinsonian patients is a well established fact clinically.[13] Our present results extend these findings to the experimental type of tremor and may provide an explanation for this phenomenon. If it is accepted that the cells recorded from in the motor cortical areas are motor in function and have a motor outflow, these results may point to the pyramidal tract as the final common path used by tremorogenic impulses to reach the spinal cord.

However, there are some alternative hypotheses that could also explain the patterns of activity seen and that cannot be completely rejected at this time. For example, in the case of cells firing in synchrony with the tremor, it is quite possible that this pattern of activity is the result of the tremor rather than its cause. In other words, the unit recorded from may be fired by the tremor through sensory afferent impulses reaching it from the moving limb. Suggestive in this regard is the report by Mountcastle[14] that, in the cat's sensory cortex, some 15% of the cells are fired by passive movements of the limb and that their optimum rate of firing seems to be at a frequency of alternating movements of some 4 to 5 per second. Whether the same is true of the motor cortex is not known. Another possibility is that both of the above hypotheses may be true depending on the area from which one is recording; the unit activity may be the result of the tremor in the sensory area and its cause in the motor cortex. From a perusal of the records, one sometimes gets the impression that, in fact, we are dealing with two different patterns of firing, one from the sensory and another from the motor cortex, even though both

groups of cells are firing in synchrony with the tremor. In the motor cortex (Fig. 4A), the cells often fire infrequently and the synchrony is short lasting. In the sensory cortex (Fig. 4B and 4C), the synchrony is more marked and longer lasting and the cells fire several times at each tremor cycle.

A third hypothesis, which is more unlikely but cannot be discounted, is that the cortical activity and peripheral tremor are not causally related but that both are produced simultaneously by a third, subcortical pacemaker with a caudally and rostrally oriented outflow.

As far as the cells that increase their rates of firing at outset of a tremor episode are concerned, their increased activity may be the witness of the general arousal that was often found necessary to initiate tremor in these animals. During long recording sessions in the dark, the monkeys would tend to become drowsy and the tremor would disappear. It was then necessary, while recording from a single unit, to arouse the animal with a sudden noise or a light shone in its eyes to obtain tremor movements. These nonspecific alerting stimuli may have been the cause of the increased rate of firing observed in some cortical cells.[7] Their even distribution in contralateral and ipsilateral areas would be consistent with this view. It is quite evident that control experiments are needed to determine which of the above explanations accounts for the phenomena observed.

SUMMARY

Lesions were placed in the brain stems of monkeys to produce an experimental postural tremor. Clinical and electromyographic studies have shown this tremor to be very similar to that seen in patients with paralysis agitans.

Microelectrode recordings of unit activity were obtained from the sensorimotor cortex contralateral to the tremor and from the ipsilateral motor cortex. The results reported suggest the direct involvement of the contralateral motor cortex in the production of the tremor movements.

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Mechanical and electrical responses of intact thenar muscles to indirect stimuli

Study of patients with pseudohypertrophic muscular dystrophy

Stella Y. Botelho, M.D., Sibyl B. Beckett, M.S., and Eleanor Bendler, M.D.

THE CHARACTERISTICS of the electrical activity of skeletal muscle which result from voluntary activity and are recorded with needle electrodes have been the subject of many reports.[1–4] Although Harvey and Masland[5] suggested in 1941 that analysis of the electrical response of indirectly stimulated muscle might be useful to both elucidate the disease process and follow the course of the disease in patients with muscular dystrophy, we are unaware of any such investigation. Recently, Glaser and Stark[6] reported normal refractory period measurments in patients with progressive muscular dystrophy and mice with hereditary primary myopathy. Sandow and Brust[7] have described the mechanical properties of skeletal muscle excised from genetic dystrophic mice. Similar studies of mechanical properties have not been reported in human muscular dystrophy.

In the present study, we have analyzed the simultaneously recorded mechanical and electrical responses of intact thenar muscle to indirect single, paired, and repetitive stimuli in patients with pseudohypertrophic (childhood) muscular dystrophy and in healthy subjects of similar age and sex. In many respects, our findings agree with those previously reported in human and mouse dystrophy, but certain differences have been found. In view of the widely accepted concept that the distal muscles of the extremity (including the intrinsic hand muscles) are spared[8] or at least are not seriously involved until late in this disease,[9] it is of some interest that significant differences from the normal were found in the thenar muscles of even the youngest patients, who were still in the walking stage of the disease.

APPARATUS

Details of the apparatus have been given elsewhere.[10] In brief, we have recorded the simultaneous electrical and mechanical responses of intact thenar muscles, which were induced to contract by percutaneous stimulation (Grass S4B stimulator, Grass SIU4A stimulus isolation unit) of the ulnar nerve. Surface electrodes were used for stimulating and recording because we were able to obtain the cooperation of the patients for repeated studies if we could assure them and their parents that needles would not be used. Furthermore, we were interested in the integrated electrical activity of the entire muscle since we were also recording the tension developed by the whole muscle. In order to record the electrical activity with high and low gain simultaneously, the muscle action potentials were amplified by two preamplifiers (Grass P5R) in parallel and led to the inputs of an electronic switch (Dumont 330), the output of which activated one beam of a

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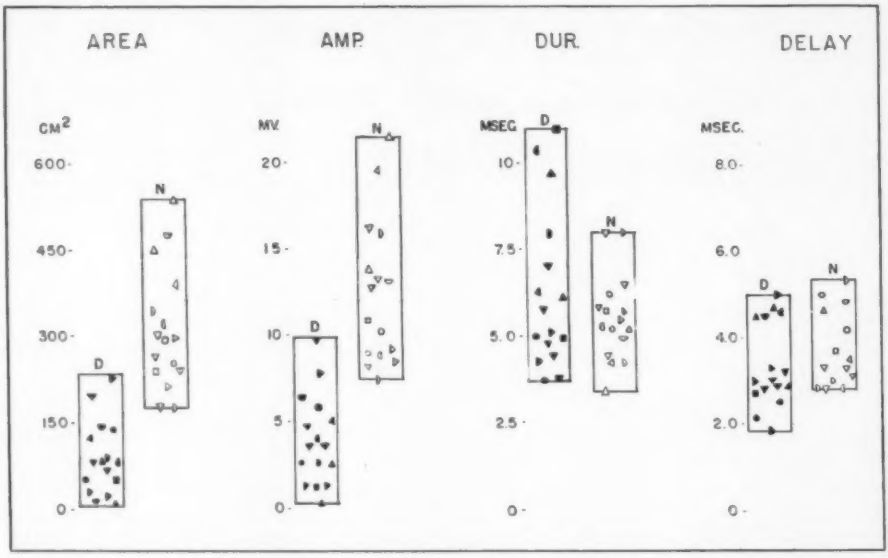

Fig. 1. Area, amplitude (amp.), duration (dur.), and delay of electrical response to single supramaximal stimulus. Amplitude was measured by planimeter and converted to square centimeters with amplification equivalent to 100 μv. per centimeter. In this and all subsequent figures, D and closed circles indicate values for dystrophy patients; N and open circles indicate values for healthy subjects. Symbols in this and Figures 2 and 3 indicate age (in years) according to the following key: semicircle base to the left, 6; semicircle base to the right, 8; triangle apex down, 10; circle, 11; square, 12; semicircle base up, 14; triangle apex to the left, 15; triangle apex to the right, 16-17; triangle apex up, 23-25.

double beam cathode ray oscilloscope (Dumont 279). Mechanical activity (isometric tension) was recorded by strain gauges bonded to a bar, to which the thumb was attached by a relatively rigid stirrup. After suitable amplification (Sentinel), the output of the strain gauge activated the second beam of the cathode ray oscilloscope. The 600-cps input to the strain gauges was not demodulated so that the mechanical record also served as the time reference. The screen of the cathode ray oscilloscope was photographed on 35-mm. film moving continuously at the rate of 1,200 in. per minute (Dumont oscillograph camera 321A). Details of the measurements we made have been outlined in a previous paper.[10] All measurements were made after the film was projected in a microfilm reader (magnification × 15, American Optical Co. 3400).

EXPERIMENTS AND RESULTS

A group of 16 male patients ages 6 to 25 years with pseudohypertrophic muscular dystrophy, (hereafter referred to as the PHMD group) were matched by age (± two months) with an equal number of healthy male subjects. In each individual, we performed experiments designed to determine the following characteristics of the indirectly stimulated muscle:

1. The number of fibers that can be recruited (electrical responses to single maximal and threshold stimuli)

2. The ability to develop tension (the mechanical response to single and repetitive stimuli)

3. The effects of activity (the changes in single responses during and after repetitive stimulation)

4. The elastic and contractile properties (the slopes of the passive and active tension-length curves)

5. Excitability (refractory period).

Throughout the entire study, supramaximal stimuli were applied to the ulnar nerve at the wrist. The intensity and duration of the stimuli varied from 107 to 128% of maximal and 0.02 to 0.8 msec., respectively, among experiments, but these stimulus parameters were constant in any given experiment.

We agree with Horvath and associates[11] that "there is no average dystrophic muscle" because, as a result of the larger variations among the patients, mean values for the PHMD group may not differ statistically from mean values for the healthly subjects. Nevertheless, in general, when the value for each patient is compared with the value in a healthy subject of comparable age, the patient value bears the same relation to the normal value as the mean of the PHMD group bears to the mean of the healthy group. For these reasons, wherever pertinent, we have presented the data so that such comparisons may be made.

TABLE 1
AREA OF MUSCLE ACTION POTENTIAL INDUCED BY THRESHOLD AND MAXIMAL STIMULI

	Subject	*Age (years)*	*Threshold mm.²*	*Maximal mm.²*	*Maximal: threshold*
Dystrophy	Gr	8	12	8,278	690
	By	17	13	3,490	269
	La	11	13	13,740	1,080
	Va	15	13	12,680	978
	Br	11	21	5,220	245
	Sh	12	27	5,200	189
	Mo	14	63	14,200	226
	Ch	25	85	670	7
	De	6	118	9,040	76
	Re	10	128	1,576	12
	Ke	21	139	8,400	60
	Li	10	279	6,760	24
	Ru	16	531	23,380	44
Healthy	Hy	8	83	30,300	369
	Wa	17	47	29,220	621
	LL	11	530	26,550	51
	Ro	15	382	39,000	102
	J.E.	11	77	26,000	338
	W.L.	12	176	29,300	165
	Du	14	62	47,200	764
	Sm	23	54	45,120	840
	Fo	6	95	34,600	362
	Gr	10	76	18,000	236
	Ar	10	105	24,100	230

All measurements at gain = 100 μv. per centimeter

Electrical response to single stimulus. With comparable gain, the muscle action potential produced by supramaximal indirect stimulation was smaller in the PHMD group than in the healthy subjects as measured by the area of the negative phase (hereafter referred to as the action potential area) (Fig. 1). The decreased area resulted from a decrease in amplitude, not duration, since the duration of the potentials in the PHMD group was never shorter than normal and was definitely prolonged in 3 patients. On the other hand, action potential area and amplitude were less in the PHMD group, the mean area and amplitude of the PHMD group being only 28 and 30% of the normal mean values, respectively. The data in Table 1 indicate that the threshold action potential area was decreased in 6 of the patients and the ratio maximal action potential area : threshold action potential area was decreased in 6 other patients.

Mechanical response to single and repetitive stimuli. The tension developed by single twitches and tetanus (30 per second for one second) was less in all the dystrophic patients, the mean developed tension of single twitches and tetanus being only 16 and 25%, respectively, that of the healthy subjects (Figs. 2 and 3). The tetanus : twitch ration was increased in 6 patients so that the mean tetanus : twitch ratio was somewhat greater in the PHMD group. In 6 other patients, the change in tension from the knee of the tension-time curve to the end of the tetanus was greater than in healthy subjects. The contraction kinetics of the single twitch were altered in the PHMD group as indicated by the prolonged latent period, prolonged plateau period, slower maximal contraction rate, and prolonged three-quarter relaxation period. The contraction kinetics of tetanus were so altered in the dystrophic patients that residual tension and three-quarter relaxation periods were prolonged. These findings are similar to those reported by Sandow and Brust[7] in mice with genetic dystrophy.

Effects of activity. Stimuli were applied with intervals of thirty seconds to five minutes as indicated in the following sequence: single;

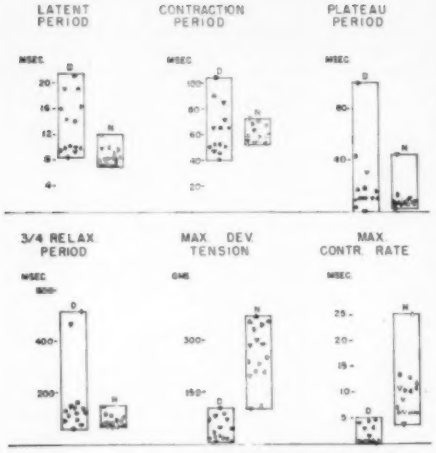

Fig. 2. Characteristics of mechanical response to single sup.maximal stimulus: latent period, contraction period, plateau period, three-fourths relaxation (relax.) period, maximum (max.) developed (dev.) tension, and maximum (max.) contraction (contr.) rate of same tension-time curve

one minute; single; thirty seconds; single; thirty seconds; repetitive twitches (3 per second for two seconds); thirty seconds; single; two minutes; tetanus (30 per second for one second); thirty seconds; single; 30 seconds; 3 per second for two seconds; thirty seconds; single; 30 seconds; single; 3 minutes; single; five minutes; single. Electrical and mechanical responses were unaltered when the interval between stimuli was at least thirty seconds (Table 2). On the other hand, in the PHMD group, there was greater variability of response and, in 6 patients, depression of single twitch tension unaccompanied by a change in the action potential thirty seconds after a conditioning train of 6 stimuli at a frequency of 3 per second (Table 2). The data in Table 3 indicate that the PHMD group showed a decline in the tension developed by successive single twitches with 3 per second stimulation. This decrease in successive twitch tension was not accompanied by a change in the simultaneously recorded action potential. On the other hand, there was a slowly progressive decrease in the size of successive action potentials with tetanus (30 per second for one second), which was of the same degree in the PHMD and healthy groups (Fig. 4 and Table 3). Confirming other reports[10,12–14] in healthy subjects, maximum potentiation of single twitch tension occurred thirty seconds after a conditioning tetanus and some degree of potentiation persisted for several minutes.

The data in Table 4 indicate that 92% of the healthy subjects showed potentiation and none showed depression of twitch tension thirty seconds after tetanus. On the other hand only 50% of the patients showed potentiation and 17% showed depression of twitch tension thirty seconds after tetanus. Furthermore, five minutes after tetanus, 42% of the healthy subjects still showed some degree of potentiation and none showed depression, but only 8% of the PHMD group still showed potentiation and 59% showed depression of

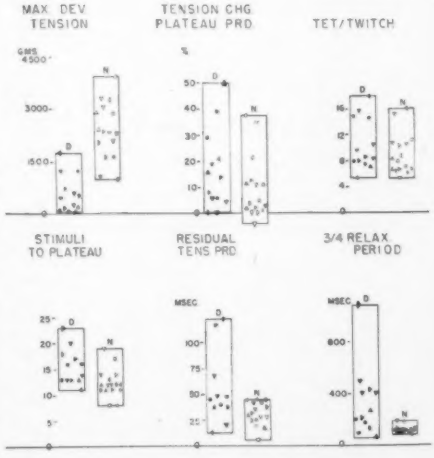

Fig. 3. Characteristics of mechanical response to tetanus (30 per second for one second): maximum (max.) developed (dev.) tension, tension change (chg.) during the plateau period (prd.), that is, from the knee of the tension-time curve to the end of the tetanus, ratio tetanus tension : twitch tension (tet./twitch), number of stimuli until plateu (that is, knee of tension-time curve) is achieved, residual tension (tens.) period (prd.) that is, from start of last potential to start of decline in tension, and three-fourths relaxation (relax.) period

TABLE 2
DIFFERENCES BETWEEN TENSION OF TEST RESPONSES (TR) AND SINGLE CONDITIONING RESPONSES (SCR) IN PERCENTAGE OF TR

Dystrophy	After SCR: One Minute	After SCR: Thirty Seconds	After 3 per second: Thirty Seconds
By	0	−30	−30
Ru	−12	−15	−12
Mo	− 8	−14	−20
Gr	− 1	− 3	− 5
Br	0	0	0
Ce	+.9	+ 4	−35
Li	0	+ 7	+13
Va	+ 1	+ 9	−37
La	+10	+ 9	0
Ke	+14	+14	+ 9
De	−11	+20	+10
Re	+27	+26	+10

Healthy	After SCR: One Minute	After SCR: Thirty Seconds	After 3 per second: Thirty Seconds
FE	−12	−10	−10
LL	− 3	− 4	+ 5
Du	+ 6	− 1	+ 4
Hy	− 5	0	+ 3
WL	−25	0	− 1
Gr	0	+ 1	+ 1
La	+ 4	+ 3	− 1
Wa	− 2	+ 3	− 1
Sm	+ 5	+ 3	+ 2
JE	+ 8	+4	+11
Ar	+18	+18	+19
RO	+33	+33	+22

TABLE 3
RESPONSES TO REPETITIVE STIMULI

	Stimulus frequency	Ratios*	Mean ± standard error: Normal	Mean ± standard error: Dystrophy
Tension/Action potential area	3 per second	1R:CR	.97 ± .02(16)	1.07 ± .04(13)
		5R:1R	1.08 ± .03(16)	.95 ± .04(12)
	30 per second	1R:CR	.96 ± .02(14)	1.12 ± .05(13)
		5R:1R	.90 ± .04(14)	.90 ± .06(12)
		15R:1R	.80 ± .06(13)	.88 ± .06(13)
	3 per second	1R:CR	1.03 ± .03(16)	1.00 ± .04(12)
		5R:1R	1.00 ± .03(16)	.80 ± .08(11)

*1R = initial response; CR = control response; 5R = fifth response; 15R = fifteenth response. Figures in parentheses indicate number of subjects

twitch tension. As reported in healthy subjects,[10,12–14] the posttetanus changes in tension were not accompanied by consistent changes in the electrical activity in either the healthy subjects or dystrophic patients. The conditioning tetanus did not alter significantly the relaxation period of the twitches after tetanus in the healthy subjects and most of the dystrophic patients. However, in 3 of the dystrophic patients, relaxation of the twitch after tetanus was greatly prolonged (Table 5). This observation differs from that of Sandow and Brust,[7] who found that previous activity shortened the relaxation period of excised genetic dystrophic mouse muscle as well as of healthy mouse muscle.

Length-tension diagrams. A single stimulus was applied when the muscle was passively placed at each of three different lengths. The passive change in muscle length was generally from greater to less abduction, and one minute was permitted to lapse after each change in length before the stimulus was applied.

Passive tension-length. At each muscle length, the PHMD group had less passive (resting) tension than the healthy subjects. This smaller passive tension was not the result of a difference in stretch reflex activity because, even with amplification of 50 μv. per 7 cm., no electrical activity was recorded from the resting muscle of either healthy or dystrophic subjects (Fig. 5). The elastic properties of a substance can be described by measurement of the slope of the passive tension-length curve (Fig. 6), either as stiffness (grams per centimeter) or its reciprocal, extensibility. From the latter portion of the passive tension-

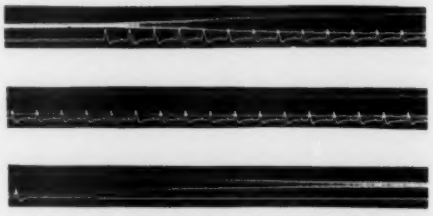

Fig. 4. Typical continuous record of electrical (lower trace) and mechanical (upper trace) responses to a train of stimuli at a frequency of 30 per second (tetanus). On the electrical recording, upward is negative and large upward deflections are action potentials. Small upward deflections preceding the action potentials are stimulus artifacts. Time (tension record), 600 cps

TABLE 4

EFFECTS OF TETANUS ON RESPONSE TO SINGLE STIMULUS

		Age (years)	Tension: Time one-half minute	Tension: After five minutes	Action potential area: Tetanus one-half minute	Action potential area: Tetanus five minutes
Dystrophic	Br	11	69	44	106	111
	Ke	21	87	132	102	115
	Gr	9	93	88	108	100
	Ru	16	100	80	115	114
	De	6	103	66	—	126
	Va	15	103	92	90	95
	Mo	14	110	86	87	103
	By	17	120	50	140	111
	Ce	17	126	104	91	75
	Li	10	133	87	108	114
	La	11	136	110	96	126
	Re	10	164	101	87	86
Healthy	Du	14	104	108	91	100
	La	17	110	91	101	88
	Wa	17	110	93	99	100
	L.L.	10	115	104	96	89
	Ro	15	119	100	68	76
	Sm	21	120	109	100	92
	Hy	9	125	105	112	96
	F.E.	6	126	126	89	92
	W.L.	11	133	110	97	100
	Gr	10	150	138	73	86
	Ar	10	185	152	79	93
	J.E.	11	187	116	103	95

All numbers are per cent of control single response before tetanus.

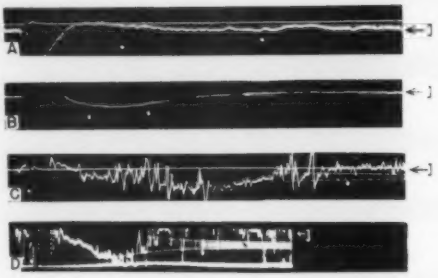

Fig. 5. Records showing three-fourths relaxation period of tension tracings (marked by dots) in a dystrophic patient (A, single twitch, and C, tetanus) and in a normal subject (B, single twitch, and D, tetanus). In all records, the electrical activity is recorded with high and low gain. Brackets indicate 100-μv. calibration for high gain traces as indicated by the arrows. Amplification varied from record to record with low gain electrical tracing and with mechanical tracing. Time, 600 cps. It should be noted that, in record C, the high gain tracing of electrical activity has been retouched to increase the contrast for reproduction.

TABLE 5

EFFECTS OF TETANUS ON THREE-FOURTHS RELAXATION PERIOD

Dystrophic	Before tetanus	Thirty seconds after tetanus	Difference	Healthy	Before tetanus	Thirty seconds after tetanus	Difference
Mo	65	53	—12	F.E.	67	79	+11
Va	74	98	+24	Ar	69	58	—11
De	83	83	0	Hy	72	72	0
By	92	62	—30	Sm	73	63	—10
Li	95	194	+109	Je	80	82	+ 2
La	104	94	—10	Gr	80	87	+ 7
Br	137	118	—19	La	83	80	— 3
Ru	147	132	— 5	Wa	85	84	— 1
Gr	154	104	—58	L.L.	85	89	+ 4
Ke	206	>650	+494	W.L.	92	97	+ 5
Re	209	>570	+361	Ro	108	74	+24

All numbers are in milliseconds.

length curves, we found the mean values for stiffness to be 89 gm. per centimeter in the PHMD group and 120 gm. per centimeter in the healthy group. Contrary to the finding of an increase in stiffness (decreased extensibility) in genetic dystrophic mouse muscle,[7] we found a decrease in stiffness (increased extensibility) in the patients with pseudohypertrophic muscular dystrophy.

Active tension-length curves were plotted from data obtained by single stimuli rather than tetanic stimuli for two reasons: [1] tetanic stimulation is more uncomfortable, and we required the cooperation of the patients and their parents for repeated studies; [2] within the physiologic limits of stretch of healthy human muscle in situ, the general shape of the single twitch tension-length curve is the same as the tetanus tension-length curve.[15] We found that active tension increased when the initial muscle length was increased in the healthy subjects but not in the dystrophic patients (Fig. 7). Differences in passive and active tension-length curves have been shown to occur with age,[15] but, in this study, the healthy subjects and dystrophic patients were carefully matched with regard to age. There were no consistent changes in the action potentials accompanying the tension changes at the different muscle lengths. It was noted that maximal voluntary abduction of the thumb in dystrophic patients was less than in the healthy subjects (Fig. 6) and that, frequently, a greater degree of passive abduction than maximal voluntary abduction of the thumb could be achieved in the dystrophic patients. These two findings suggest that the weakness, as objectively measured by maximal induced adduction of the thumb, is also present in the thumb abductors of even the youngest patients, who show no other clinical evidence of involvement of the intrinsic hand muscles.

Refractory period. One method of determining excitability of a tissue is to measure the refractory period by applying a test stimulus at varying intervals after a conditioning stimulus. In this series of experiments, pairs of conditioning and test stimuli of identical intensity and duration were applied at thirty-second intervals in the following sequence: single

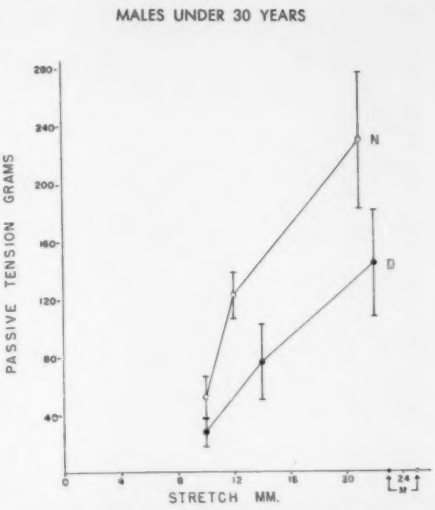

Fig. 6. Passive (initial) tension-length diagram. ○ on horizontal axis corresponds to maximal adduction of thumb (minimal stretch of adductor pollicis). M corresponds to maximal voluntary abduction (maximal stretch of the adductor pollicis). Vertical bars correspond to the standard errors of the means.

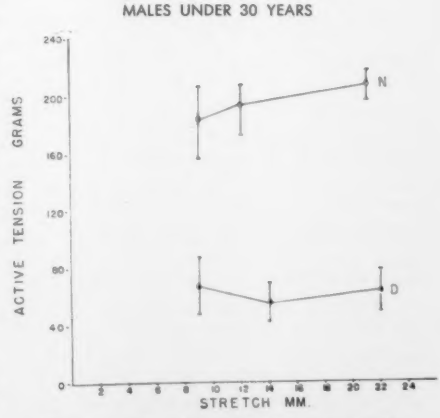

Fig. 7. Active (developed) tension-length diagram. ○ on horizontal axis corresponds to maximal adduction of the thumb (minimal stretch of adductor pollicis); maximal stretch same as in Figure 8. Vertical bars indicate the standard errors of the means.

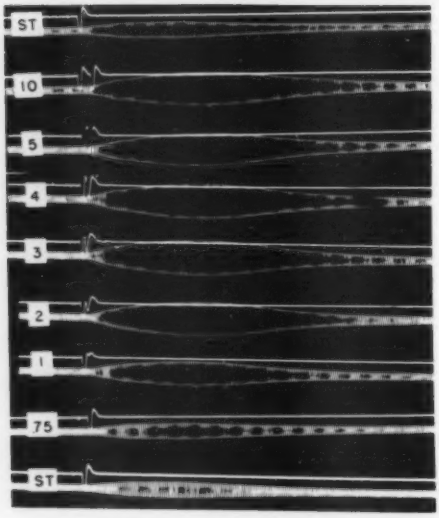

Fig. 8. Typical records of electrical (upper trace) and mechanical (lower trace) responses to single (ST) and paired stimuli (conditioning-test shock intervals in milliseconds to the left). On the electrical recording, negative is downward, large downward deflections are the action potentials, and small downward deflections preceding the action potentials are the stimulus artifacts. Time (tension record), 600 cps

test; single test; paired with conditioning test shock intervals varying from 10 to 1 msec. in 1-msec. steps and from 1 to 0.25 msec. in 0.25 -msec. steps (Fig. 8). In each individual, we determined the maximum potentiation and the long and short refractory periods (Table 6) from a graph relating the maximum developed tension to the conditioning-test shock interval (Fig. 9). We chose to determine the refractory period values from the mechanical rather than the electrical response for reasons that have been given elsewhere,[16] but which may well be summarized here. Unlike other studies of the refractory period in human muscle[6,17] in which needle electrodes have been used, our studies were done with surface recording electrodes. When action potentials are obtained from many fibers, the test potential becomes superimposed upon the conditioning response when the interval between shocks is less than 10 msec. (Fig. 8). Thus, there is an apparent decrease in the electrical response to the test stimulus at a conditioning test shock interval when there is no decrease in the simultaneously recorded mechanical response (Fig. 9). We would emphasize that our refractory period figures are not necessarily those for absolute refractory period since we did not alter the intensity of the test stimulus. Furthermore, we do not know from these studies whether we are measuring the refractory period of nerve, neuromuscular junction, or muscle. We assume that not all the nerve-muscle units have the same refractory period, and, because we are recording from many muscle fibers, we believe that the first decrease in tension which occurs as the interval between conditioning and test stimuli is shortened results from lack of response of nerve-muscle unit with the longest refractory period.

We, therefore, arbitrarily designated the conditioning-test shock interval when the developed tension was 90% of the maximal developed tension as the long refractory period (Fig. 9). We believe that this corresponds to the time after a conditioning stimulus when some of the nerve-muscle units do not respond. The short refractory period corresponds to the time after a conditioning stimulus when the developed tension is only 60% of the sum of 2 single test responses (Fig. 9). It marks the time interval after a conditioning stimulus when all the nerve muscle units are refractory to a given supramaximal stimulus.

No differences between the PHMD and

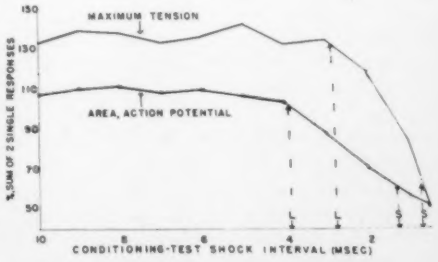

Fig. 9. Typical plot of electrical and mechanical responses and conditioning-test shock intervals to determine refractory period. L and S are long and short refractory periods, respectively (see text).

TABLE 6
RESPONSE TO PAIRED STIMULI

	Mean ± Standard Error	
	Healthy	*Dystrophy*
Refractory period (msec.)		
long	4.8 ± 0.64 (16)	5.5 ± 0.82 (14)
short	0.7 ± 0.28 (16)	0.67 ± 0.06 (14)
Potentiation of tension (Per cent, 2 single twitches)	156. ± 6.2 (15)	195. ± 24. (14)
Interstimulus interval (msec.) producing maximum potentiation	6. ± 0.64 (15)	7. ± 0.64 (14)

Figures in parentheses indicate number of subjects.

healthy groups were seen, although there were greater variations in the maximum degree of potentiation in the dystrophic patients. Our value for the short refractory period, which marks the time after a conditioning stimulus when all the muscle fibers are refractory, agrees with the refractory period values for the human thumb muscles reported by Hoefer and associates.[17] Our measurements of the refractory period confirm the previous report[6] that excitability of the muscle fibers is unaltered in patients with PHMD.

COMMENTS

The diagnosis of pseudohypertrophic muscular dystrophy is based upon its well known clinical picture. In the present study, we determined objectively that the intact thenar muscles of all the patients, even those still in the walking stage, were weaker than normal. This weakness was characterized by a decrease in isometric tension and was associated with decreased stiffness, slowing of contraction and relaxation, and inability to sustain tension during and after repetitive stimulation. Factors that could result in a decrease in the isometric tension developed by a muscle are [1] a decrease in the number of contracting muscle fibers, [2] increased temporal dispersion, [3] increase in noncontractile tissue possessing abnormal elastic properties, and [4] inability of the contractile material to generate tension.

From analysis of the electrical response to a single stimulus (Fig. 1), it is evident that not only are there fewer active fibers but that there also may be increased temporal dispersion in some patients, as indicated by the prolonged duration of the action potential in some of the dystrophic patients. Increased temporal dispersion could account for the smaller amplitude of the action potential, but the area of the action potential would not be decreased if temporal dispersion were the sole factor. The smaller action potential area could result from at least 3 factors, alone or in combination: [1] fewer contracting fibers, [2] increase, either relative or absolute, in the amount of nonmuscle material, such as edema, fat, or skin, interposed between the recording electrodes and active tissue, [3] decrease in the electrical potential contributed by each muscle, as might occur if the electrical properties of the muscle fibers (membrane potential, resistance, capacitance) were altered, and [4] decrease in the electrical potential contributed by each muscle fiber, as might occur if the fibers were smaller in size. We cannot differentiate between these factors that could produce a smaller action potential in the present study. Nevertheless, it is unlikely that smaller fibers per se could account for the diminished potential since in all stages of the disease very large and very small muscle fibers are scattered haphazardly throughout the muscle.[18] The electrical properties of human dystrophic muscle have not as yet been reported, so it is possible that abnormal electrical properties might account for the decreased size of the integrated action potential that we recorded with surface electrodes. With regard to the number of active fibers, the data in Table 1 are of interest; 6 of the patients showed a decrease in the ratio of maximal action potential to threshold action potential, although the size of the threshold potential was not decreased. In these patients, the nonmuscle

tissue interposed between recording electrodes and active tissue must have been the same with threshold and maximal stimulation; therefore, fewer than normal fibers were activated when the stimulus intensity was varied from the threshold to maximal. It is of some interest that the youngest patient we studied (De, age 6 years) was in this group showing evidence of a decrease in the number of muscle fibers; 6 other patients showed decrease in size of the threshold and maximal action potential so that the ratio maximal action potential area : threshold action potential area was normal. In these patients, not only could there have been a decrease in the number of fibers but there also could have been an increase in the noncontractile substance interposed between recording electrodes and active fibers.

Regardless of whether Hill's[19] theory, recently modified by Sandow,[20] that the noncontractile tissue of muscle acts as a series elastic element or Goodall's[21] theory that the noncontractile tissue acts as a parallel elastic element is correct, either an absolute or relative increase in noncontractile tissue could produce a decrease in isometric tension if the noncontractile tissue were less stiff than normal. We found that the intact thenar muscles of the patients with pseudohypertrophic muscular dystrophy were less stiff than muscles of healthy subjects. We can only speculate about the reasons for this abnormality in the elastic properties of dystrophic muscle. Human pseudohypertrophic dystrophic muscle may be less stiff than normal because the muscle and/or nonmuscle tissue has abnormal elastic properties. It is well known that there is either an absolute or relative increase in nonmuscle tissue in dystrophic muscle, but, despite recent reports by Beckett and Bourne,[22] knowledge of the exact nature of the nonmuscle tissue in pseudohypertrophic muscular dystrophy awaits the availability of more refined histochemical technics.

We believe that the nonmuscle tissue in human pseudohypertrophic dystrophic muscle differs from that found in genetic dystrophic mouse muscle, experimentally denervated rat muscle, and immobilized rabbit muscle because, in these three states, increased stiffness is found.[7,23,24] It is possible but not probable that the difference in elastic properties of human pseudohypertrophic and genetic dystrophic mouse muscle may be the result of technical differences, since the latter was not examined in vivo. It is also unlikely that the difference in stiffness results from the fact that the mouse dystrophy was studied in a different stage because decreased stiffness was found in all the patients regardless of the stage of the disease. The decreased stiffness that we observed is not inconsistent with the contractures, so characteristic of childhood dystrophy, where the shortened muscles are the relatively strong muscles (for example, gastrocnemius vs. anterior tibial) that have not received adequate therapy to prevent deformity. It would appear from the results of the present study that the crippling deformities in childhood dystrophy result not from replacement of muscle tissue by stiffer nonmuscle tissue but from active contraction of the relatively stronger muscles. The slowed relaxation of the dystrophic muscle, as indicated by the prolonged three-fourths relaxation period (Figs. 2, 3, and 5), further augments the shortening since muscles in situ contract by asynchronous repetitive firing of the motor units. The prolonged relaxation period was not directly correlated with the electrical activity of the muscle when recorded with surface electrodes (Fig. 5). We, of course, were unable to detect asynchronous contraction of individual muscle fibers with surface electrodes. However, it is difficult to believe that asynchronous firing of individual muscle fibers could contribute sufficient tension to account for the prolonged relaxation period for the following reasons: [1] Asynchronous motor unit activity as seen in the healthy subject after tetanus (Fig. 5) did not produce sufficient tension to prolong the relaxation period. On the other hand, a similar or even lesser degree of asynchronous motor unit activity after tetanus was accompanied by a prolongation of the relaxation period in the dystrophic patient (Fig. 5). [2] Tension was never recorded as a result of a threshold stimulus (as judged by the action potential). Activity such as 30 per second for one second tetanus did not shorten the relaxation period. On the contrary, in some of the dystrophic patients, the three-fourth relaxation

period was prolonged by such activity (Table 5).

Sandow and Brust[7] have reported that activity decreases the relaxation period of both the genetic dystrophic and normal mouse muscle. Although these authors have pointed out to us in a personal communication that the degree of activity which they used in their studies (about 1 per second stimulation) was much less than that of the present study, it is still possible that the effects of activity upon dystrophic human muscle may differ from those of genetic dystrophic mice. It has been suggested that genetic mouse muscular dystrophy is similar to pseudohypertrophic dystrophy.[7,25] However, we believe that the dissimilar findings with regard to stiffness and activity indicate that the disease process may not be identical in the two conditions. We would emphasize that study of human dystrophic muscle must be made if the cause of the human disease is to be elucidated. Other evidence that genetic dystrophy in mice differs from pseudohypertrophic dystrophy in human beings has been reported.[26]

Abnormal contraction kinetics (prolonged latent period, slower contraction rate, and prolonged three-fourth relaxation period), which we observed in the dystrophic patients, can be interpreted to mean an alteration in the intrinsic properties of the muscle fibers only if other possible mechanisms are excluded. A decrease in muscle temperature could produce changes in contraction kinetics similar to those we observed in the dystrophic patients. Maclagan and Zaimis[27] have reported that cooling of cat muscle in situ 6° C. will produce a decrease in tension of 22% and prolongation of the over-all twitch duration of 19%. It is possible that the intact thenar muscles of the dystrophic patients were 6° C. cooler than that of normal subjects under the same experimental conditions, but the mechanism for such a difference is obscure. Furthermore, if the alterations in the contraction kinetics were due to decreased temperature alone, we would expect the rise in temperature produced by tetanus to decrease the latency and speed the contraction and relaxation of the posttetanus twitches. Such changes did not occur in either the healthy or PHMD group. We believe the altered contraction kinetics do indicate that the intrinsic properties of the contractile material are abnormal in PHMD.

Certain observations we have made in the dystrophic patients in this study are best explained by the hypothesis that the dystrophic muscle fibers have abnormal intrinsic properties such that the contractile substance has decreased ability to produce tension:

The abnormal flat active tension-length curve (Fig. 7). This finding indicates that, even within the physiologic range of stretch, the muscle fibers cannot generate greater tension when the initial length and tension are increased.

The abnormal tension response to a train of repetitive single stimuli such that there is a decrease in tension developed by the fifth twitch which is unaccompanied by a decrease in the action potential (Table 3). This finding indicates that the decreased twitch tension does not result from a decrease in the number of active contractile units that respond to successive stimuli. Although a similar observation has been made in some patients with myasthenia gravis, others show a decrease in tension in response to repetitive single stimuli which is associated with a decrease in the simultaneously recorded action potential.[28]

The abnormal response (depression of twitch tension) to a specific degree of induced activity that in normal muscle produces prolonged potentiation of twitch tension (Table 4). Although the mechanism for posttetanic potentiation of twitch tension is not known, the consensus is that this phenomenon is of a biochemical nature.[10,12–14] Posttetanic potentiation of twitch tension, as pointed out by Johns, Grob, and Harvey,[29] is to be distinguished from posttetanic facilitation, which may be seen in patients with myasthenia gravis. This posttetanic facilitation is of short duration, is accompanied by an increase in the size of the action potential, and indicates a facilitation of neuromuscular transmission. The abnormal depression of twitch tension unassociated with depression of action potential after a given degree of tetanus which we observed in the dystrophic patients is not the same phenomenon as the posttetanic exhaustion that Desmedt[30] has described in patients with myasthenia gravis. In the latter case, tetanus

produces a decrease in size of the action potential, indicating a depression of neuromuscular transmission. In view of the report that human dystrophic muscle contains less potassium than does normal human muscle,[11] it is of some interest that absence of posttetanic potentiation has been found in cats with tissues acutely depleted of potassium.[31]

SUMMARY

We have determined that objectively measured differences in skeletal muscle exist between patients with pseudohypertrophic muscular dystrophy and healthy subjects of the same age and sex. Skeletal muscle weakness is associated with slowing of contraction and relaxation, decreased stiffness, and inability to sustain tension during and after induced repetitive activity. From the data, we conclude that, in pseudohypertrophic muscular dystrophy:

1] Weakness of intrinsic hand muscles can be objectively measured early in the disease.

2] The weakness of the muscle results from a decreased number of contracting muscle fibers and inherent decreased ability of the contractile tissue to generate tension.

3] The elastic properties of the muscle (contractile and/or noncontractile tissue) are changed so that the muscle is less stiff. This change in extensibility differs from that in mammalian denervated and immobilized muscle.

4] Different characteristics, particularly with regard to stiffness and the events after tetanus, of the muscle in pseudohypertrophic muscular dystrophy and those reported in genetic dystrophic mouse muscle suggest that the disease process differs in these two conditions and emphasizes the fact that human dystrophic muscle must be studied in order to elucidate the disease process.

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CASE REPORT

Postprandial hypoglycemia presenting as a neurologic problem

Warren L. Belding, M.D., and David A. Freedman, M.D.

MANY AUTHORS[1–6] have commented on the wide variety of neurologic and psychologic abnormalities that may occur as a result of hypoglycemia. Particularly in the early phases of this metabolic disturbance, its manifestations may readily be confused with those of psychoneurosis. One of the features of the present case is precisely such a confusion in diagnosis. We feel this instance of a not uncommon phenomenon to be of interest, however, not simply because of the difficult differential diagnostic problem but more particularly because of the etiology of the patient's hypoglycemia. While the occurrence of low blood sugar in the delayed phase of the dumping syndrome has been reported frequently,[2,7–13] we have been able to find only one instance in the literature in which so severe a neurologic reaction as we report has been noted.[3] In addition, our patient presents evidence to support Berry's[1] suggestion that a tendency to hypoglycemia may precede, if not even be of etiologic significance in, the development of peptic ulcer.

CASE REPORT

First admission. A 34-year-old male school teacher and factory worker was admitted in a stuporous state to the Neurologic Service of the New Orleans Veterans Administration Hospital on March 5, 1957.

Twelve hours before admission, after a large meal, he had taken a sleeping pill and lain down. About two hours later, he called his wife and told her that his vision was dim and that he felt "numb all over" and was paralyzed. His wife noted that he was having difficulty in pronouncing words correctly and that his left hand was jerking. The patient, however, remembered nothing until he awoke in the hospital; he had been transported some 65 miles by ambulance.

Past history revealed that fifteen years before, while in the Navy, he had been hospitalized for "encephalitis lethargica." For a like period, he had suffered with stomach trouble. He experienced frequent recurrences of epigastric pain as well as several episodes of hematemesis and melena. According to his wife, during the abdominal pain, he often "passed out" and "gasped for breath." Five months before the present admission, after a gastrointestinal series revealed a benign prepyloric ulcer, subtotal gastrectomy and gastrojejunostomy were done. After this procedure, there was a rapid recurrence of symptoms. He was unable to return to work because of persisting abdominal pain and nausea as well as episodes of generalized weakness. He had paresthesias encompassing his whole body and blurring of vision. A gastrointestinal series done three months after the operation revealed no marginal ulcer or other abnormality. In the interval up to his coming to our service, he sought advice from a variety of physicians, none of whom were able to help him.

Examination on admission revealed a well-developed adult male who could be aroused only with difficulty. Blood pressure was 165/

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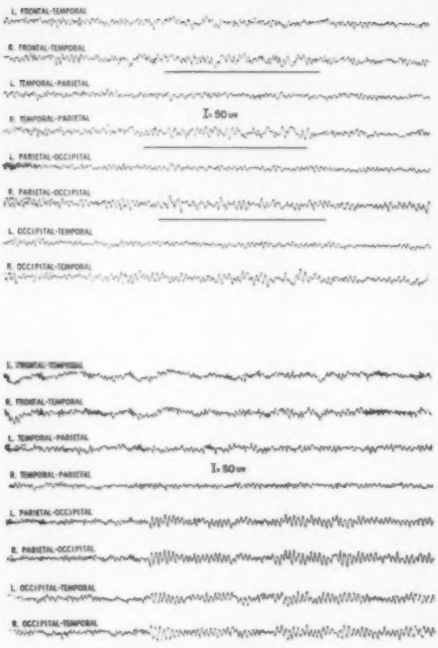

Fig. 1. (*Top*) Electroencephalogram on admission showing right temporoparietal slow wave focus. (*Bottom*) Normal waking electroencephalogram ten days later

115. General physical examination was within normal limits. Pupils were slightly dilated but reacted well to light; the optic fundi were not remarkable. The tendon reflexes in the lower extremities were symmetric and somewhat hyperactive; there were no pathologic reflexes. The cremasteric reflexes were active. The abdominal reflexes were absent, presumably because of a large surgical scar. The remainder of the neurologic examination revealed no abnormalities.

While his sensorium cleared completely within an hour of admission, he denied any recollection of the trip to the hospital. His subsequent hospital course was entirely asymptomatic. Blood pressure returned to normal levels, and the neurologic findings remitted.

Urinalysis, peripheral blood examination, serologic test for syphilis, blood urea nitrogen, fasting blood sugar, serum electrolytes, total protein, albumin-globulin ratio, and liver function studies were all within normal limits. Lumbar puncture revealed normal dynamics; cerebrospinal fluid protein was 33, sugar 94, and chlorides 137. The colloidal reaction was 0^{10} and the Kolmer negative. Skull and chest films were reported as normal. An electrocardiogram was interpreted as consisent with but not diagnostic of an old posterior wall infarct. Shortly after admission, an electroencephalogram showed right temporoparietal slow wave focus; ten days later, a second tracing was within normal limits (Fig. 1). A gastrointestinal series that was made revealed only evidence of the earlier surgery.

Treatment consisted of a bland diet with 6 feedings per day, as well as Amphojel, Pro-Banthine, and Sparine. He was discharged on the sixteenth hospital day with the advice that he continue this regimen.

Interim history. Within a few days of his return home, he experienced a recurrence of cramping abdominal pains, weakness, and dizziness. Shortly thereafter, while at work, he had a blackout spell. In retrospect, he recalled that this occurred after he ate two candy bars. He remained weak and dizzy for two days and noted frequent blurring of vision as well as occasional diplopia. He began to lose his balance and sense of direction. Blackout spells increased in frequency and were usually preceded by crampy abdominal pains and a feeling of weakness. At these times, he craved sweets. He made a practice of carrying candy bars with him wherever he went and instructed his wife always to have pastries on hand.

Three months before his second admission, again while at work, a weak spell was followed by an episode of unconsciousness which lasted a few minutes. When he attempted to get up, he had a second episode. Neurologic examination done elsewhere at this time revealed marked ataxia. Gross tremor of the head and arms and slight motor aphasia were found. An exhaustive medical and neurologic workup at a local hospital was unrevealing, and the patient was discharged with the diagnosis of encephalopathy of unknown etiology. He was given Dilantin and phenobarbital for his "blackout spells."

During the following month, he continued to experience frequent episodes of abdominal

pain, loss of balance, failing vision, and cramping in his legs. The episodes seemed to be most severe after supper. However, they increased gradually in both frequency and duration, so that at times he felt continuously weak and sleepy for two to three days. Between episodes, he felt well.

Second admission. The patient was again admitted to the Neurologic Service on September 12, 1957. He complained of weakness, blurring of vision, and diplopia as well as malaise. Abnormal findings on admission were limited to the neurologic examination. He was unable to stand unsupported. Speech was slurred, the gag reflex was symmetrically diminished, and swallowing was difficult. Coarse nystagmus was noted on lateral gaze to either side. Tone in the lower extremities was increased, but the deep tendon reflexes were elicited only with difficulty. There were no pathologic reflexes. Sensory examination was not remarkable.

Improvement was again rapid. On the fourth day, his physical status was entirely within normal limits. However, he remained confused and erratic in behavior. Routine laboratory studies were again unrevealing. Urinary and blood lead levels were within normal limits, and a smear of the peripheral blood showed no basophilic stippling (the patient was employed in the manufacture of tetraethyl lead). A fasting blood sugar was 90 mg. per cent and another blood sample drawn when he thought he was going to have a spell contained 98 mg. per cent. Three and a half hours after eating, blood sugar was 102 mg. per cent. Serial blood sugar levels, determined during a twenty-hour fast, were all in the normal range.

Another gastrointestinal series was not remarkable.

An electroencephalogram three weeks after admission was interpreted as "definitely abnormal; moderately slow." Five weeks later, another electroencephalogram was regarded as "probably abnormal (fast); the previously noted focus is no longer in evidence."

The early hospital course was extremely erratic. His mood varied unpredictably from severe depression to euphoria. Several times, at night, he was found wandering in the hallway confused and trembling. His speech was

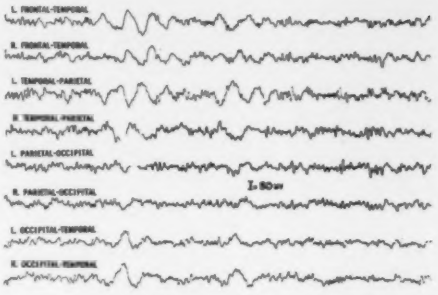

Fig. 2. Grossly abnormal electroencephalogram at time of patient's second admission

frequently incoherent. Two weeks after admission, his behavior had returned to normal, and, four weeks later, he was considered well enough to be sent home on leave. During the sixth week of his absence from the hospital, he again began to note weakness, malaise, episodes of abdominal pain, and difficulty in standing.

Examination upon his return revealed him to be again confused and dazed. As previously, he had diplopia and blurring of vision. Vital signs and general examination were within normal limits. On neurologic examination, the pupils were found to be symmetrically dilated but reactive to light. There was nystagmus on lateral gaze to either side. Speech was again slurred and stammering. The Romberg sign was present. Definite weakness of the left side, together with increased tendon reflexes and a Babinski sign on that side, was noted. Sensory examination revealed bizarre and inconstant findings. The patient's sensorium was clouded. An electroencephalogram done at this time was grossly abnormal (Fig. 2). Again, improvement was rapid with regard to both clinical findings and electroencephalogram.

At this time, the records of his hospitalization in 1942 for "encephalitis lethargica" were obtained and reviewed. It was learned that he had been admitted because of an episode of hematemesis with no previous history of gastrointestinal symptoms. While in the hospital, he was noted to have nystagmus on extreme lateral gaze and to stammer on initiating a sentence. He was described as "restless when awake and drowsy most of the time." Despite

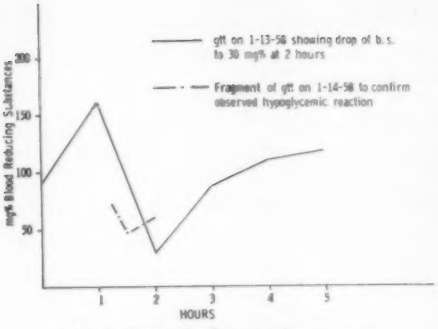

Fig. 3. Patient's glucose tolerance test

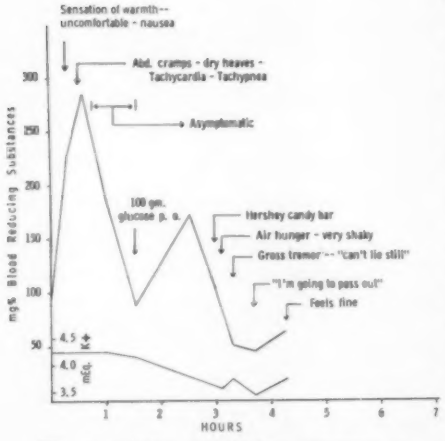

Fig. 4. Relation of subjective symptoms to blood surgar over a four-hour period

a normal spinal fluid survey, he was discharged with the diagnosis of encephalitis lethargica. Three weeks after this admission, he was studied at another naval hospital where his problem was considered to be gastrointestinal.

The patient described many episodes of severe abdominal pain during the years before his gastrectomy; he denied, however, ever having experienced loss or alteration of consciousness during that period. He commented, "If I just didn't have to eat, I'd be all right. I get deathly ill every time I eat."

At this time, a glucose tolerance test (Fig. 3) revealed a drop in blood sugar at two hours to 30 mg. per cent. In order to clarify the factors producing the hypoglycemic reaction, the blood sugar was followed after meals and/or standard glucose tolerance tests done under a variety of conditions. These included [1] various diets, [2] changes in body position during the tests, and [3] variations in the amount of exercise in the course of the tests. The patient consistently showed hypoglycemia after oral glucose or diet containing usual amounts of carbohydrate and fluid if he maintained an erect posture or exercised during most of the test. Symptoms seemed to fall into 2 groups. [1] Within thirty minutes after ingestion of food or glucose, he noted colicky abdominal pain, an uncomfortable sensation of warmth, paresthesias of his fingers, air hunger, tachycardia, nausea, and, sometimes, "dry heaves." His blood pressure and respiratory rate rose (the dumping syndrome, early postprandial symptoms). [2] One and one-half to two hours after eating, he would have marked weakness, gross tremor, stammering, and the feeling that he was about to "pass out." This phase would be accompanied by hypoglycemia. In association with it occurred a progressive drop in serum potassium (Fig. 4). An intravenous glucose tolerance test (0.5 gm. of glucose per kilogram of body weight administered as 20% solution within thirty minutes) followed the normal pattern up to the two-hour point. However, the blood sugar continued to drop and was still at the lowest limits of normal after four hours. (It is of interest that a similar pattern was observed by one of us[14] in a study of glucose tolerance in schizophrenia.)

Significant electroencephalographic changes could not be induced during acute studies such as that illustrated in Figure 4. The only change obtained under these conditions is some acceleration of the dominant frequencies. It would appear that hypoglycemia must be continued for extended periods if the electroencephalogram is to be altered. This statement applies only to that electrical activity that is accessible to scalp leads.

The patient was maintained for some six months on a diet consisting of 125 to 150 gm. of protein, 200 to 250 gm. of fat, and 100 gm. of carbohydrate. He was allowed no fluids with meals. On this regimen, postprandial blood sugar curves were consistently within

the normal range, and he continued asymptomatic during the period.

However, because of the exigencies of his job, he was unable to remain supine after each of his many feedings. Episodes of hypoglycemia recurred and were of sufficient severity so that, on one occasion, he wrecked his car and was arrested for drunken driving. His sensorium remained disturbed for eight days. At this time, at another hospital, the gastrojejunostomy was closed and the stomach remnant anastomosed to the duodenum. Four months later, he has gained 40 lb. in weight and continues asymptomatic.

DISCUSSION

Most attempts to explain the dumping syndrome have attributed the metabolic disturbance to a decrease in gastric emptying time[2,6,7,11,15,17,18] and overloading of the jejunum.[7,19] This in turn results in rapid absorption of carbohydrate with consequent pouring out of insulin,[13,16,20,22] decrease in plasma volume,[11,21,23] and changes in autonomic function. Medical treatment directed at the rapid gastric emptying will usually alleviate both the early and late (hypoglycemic) phases of the syndrome. In the vast majority of instances, a combination of a low carbohydrate–high protein dry diet, anticholinergic drugs, and maintenance of the supine position for thirty to sixty minutes after eating is sufficient prophylaxis. When, as in our patient, this does not suffice, Hinshaw, Stafford, and Jorgensen[28] and Abbott, Krieger, and Levey[29] have proposed reducing the size of the gastric stoma so as to slow the food stream mechanically. The good result that followed such a surgical revision in this case is consistent with their reports.

While the relevance of the mechanical effects of surgery in the production of the dumping syndrome cannot be doubted, a considerable body of data exists which indicates that a tendency to hypoglycemia occurs in ulcer patients before operation. In various series,[1,2,8,13,24–27] from 16 to 70% of patients with peptic ulcer have been found to present an abnormally marked and prolonged hypoglycemic phase after the ingestion of glucose. On this basis, it would seem justifiable to conclude that the mechanical complications serve only to aggravate an already existing problem.

An even more provocative consideration has been raised by Berry,[1] who feels that repeated episodes of hypoglycemia may actually be of etiologic significance in the development of peptic ulcer. In a review of 4,103 cases of diabetes reported during the preinsulin era, he failed to find a single instance associated with peptic ulcer. Since the introduction of insulin, he finds the actual incidence of peptic ulcer in diabetics to be 0.77% as against an expected incidence of 3.5%. By way of further confirmation, studies by Selye, Stehle, and Collip[30] in the rat and Poth and Fromm[31] in the dog may be cited. The former produced gastric erosions and the latter peptic ulcers in their animals by maintaining hypoglycemia.

Our patient's history, taken together with these considerations, leads us to feel that a tendency to hypoglycemia may well have been the initial manifestation of the metabolic disturbance that led to his ulcer. In this connection, it is entirely possible that an evaluation of this man's response to ingested carbohydrate before surgery might have modified his surgical and postoperative management.

From both the neurologic and psychiatric standpoints, our patient presented features that seem to us equally as provocative as his gastrointestinal problem. That severe hypoglycemia will result in neurologic and behavioral disturbances is too well known to require discussion. The particular problems with which we had to deal in this case were, first, the occurrence of focal changes on both neurologic examination and electroencephalographic study during prolonged periods of lowered blood sugar and, secondly, the striking behavioral characteristics of our patient during normoglycemic as well as hypoglycemic periods.

Meyer and Portnoy[32] have recently investigated the occurrence of focal neurologic signs in the presence of generalized metabolic disturbance. These workers induced hypoglycemia in both human beings and animals known to have regional embarrassments of the cerebral circulation. While their subjects were free of clinically detectable neurologic abnormalities during normoglycemic periods, they consistently showed signs and symptoms referable to the known areas of vascular insufficiency when their blood sugars were lowered.

Personality changes in association with hy-

poglycemia are, again, too well recognized to require further comment here. From a differential diagnostic standpoint, however, difficulty arose for us in the distinction between that which was secondary to hypoglycemia and that which antedated this metabolic disturbance and may even have been of significance with regard to its etiology. The patient presented many of the personality features Alexander[33] associates with ulcer patients. He was extremely ambitious and hard driving and yet, at the same time, quite dependent on his wife and authority figures for support and approval. Thus, for many years he held two jobs. It is of interest that he first described himself to us as a high school teacher. Later, it developed that he was a substitute instructor in physical education in a high school but that his principal source of income was a job as a semiskilled laborer in a chemical plant. He was also attending college as a candidate for a bachelor's degree. In all of these activities, he was repeatedly incapacitated by his ulcer. Like Alexander, we are inclined to feel that both these characteristics and his ulcer are symptomatic of an unconscious psychopathologic process. Garland's[34] recent review of "endogenous hypoglycemia" may be cited in this connection. He notes striking similarities in clinical characteristics, both psychologic and metabolic, among individuals with hypoglycemia after gastrointestinal surgery and those whom he classifies as "psychosomatic" in the etiology of their disturbance. While members of these two groups are frequently confused with one another, they are, according to Garland, readily distinguished from another group with "endogenous hypoglycemia," that is, patients with pancreatic adenomas.

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CASE REPORT

Some observations on hemiballismus

Stephen F. Bedwell, M.D.

THE 330 cases of hemiballismus reported in the world's literature have delineated the common clinical picture, [1–5] pathology,[6–10] pathophysiology,[11–13] and prognosis.[14–16] In recent years, variations have been reported.[17] To this latter group, the present study adds 2 further cases, each with a unique character. The first case is that of a woman with 3 transient episodes of ballistic movement, each associated with a rise in blood sugar. The second is a case of hemiballismus secondary to a discrete tuberculoma in the corpus luysi.

CASE REPORTS

Case 1. M.C. is a 65-year-old Negro woman who is seen regularly in the Neurology Clinic of the Baltimore City Hospitals. She has a father who is blind, possibly from glaucoma, a sister with glaucoma and hypertension, and another sister with hypertension.

The patient has had diphtheria, typhoid fever, and, in 1919, influenza. In 1922, after twelve years of uneventful pregnancies, she had a faint, blowing, basal systolic murmur and a blood pressure of 165/115. By 1938, she had lost the sight of her left eye because of glaucoma. At this time, her blood pressure was 210/110 and her heart was enlarged. She had a rough basal systolic murmur. Blood sugar, nonprotein nitrogen, and urine were normal.

She showed symptoms and signs of congestive heart failure between 1952 and 1955. During this period, blood pressure remained in the 210/100 range, a serologic test for syphilis was negative, fasting blood sugar was 77 mg. per cent, and urine was normal.

First episode. In 1955, at age 60, she first noted involuntary movements of her right leg. Shortly thereafter, she became clumsy with her right hand and was unable to pick up or hold objects. This progressed to wild, uncontrollable gyrations. She was admitted to the Baltimore City Hospitals, where physical examination revealed a blood pressure of 190/60; pulse, 78; and respirations, 22. Her speech was slurred. She had an artificial left eye and glaucomatous change in the right eye. Her heart was enlarged, and she had a rough basal systolic murmur. Continuous facial grimacing and wild involuntary movements of the face, neck, and extremities were noted on the right. There was marked weakness in flexion of the right elbow and in the right grip. With the exception of an absent left ankle jerk, the reflexes were symmetric and the plantar responses flexor.

Admission laboratory studies showed a blood sugar of 450 mg. per cent, a urine sugar of 4+, and a carbon dioxide combining power of 26 mEq. per liter. Other chemical findings and roentgenograms were normal aside from an enlarged heart on the chest film.

While she was in the hospital, her movements gradually subsided over a four-week period; coincident with the abatement of her movements, her blood sugar returned to normal levels. However, during this time, she was treated for fourteen days with decreasing doses of insulin ranging from 160 to 0 units of regular insulin per day. After the movements had ceased and her fasting sugar had become normal, a glucose tolerance test was performed with the results shown in the box.

After discharge, only minimal choreoathetotic movements persisted.

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Results of Glucose Tolerance Test

	Blood sugar	*Urine sugar*
Fasting	72	0
½ hour	130	?±
1 hour	193	trace
1½ hours	210	+
3 hours	131	?±
4 hours	81	0

Second episode. During the middle of March 1955, the patient had a short period of bilateral chorea of moderate degree which cleared spontaneously one week after onset. At the zenith of her movements, her fasting blood sugar rose to 106 mg. per cent from a previous level of 60 to 70 mg. per cent. After cessation of the movements, blood sugar returned to 60 to 70 mg. per cent without insulin therapy. For the next year and a half, only minor choreoathetotic movements of the hands and occasional facial grimacing remained.

Third episode. In September 1956, the patient was brought to the hospital with wild, flailing movements of her left extremities. These had come on suddenly one week before admission.

On examination, the previous eye and cardiovascular findings were unchanged. She now showed motor weakness on the left and forceful left-sided involuntary movements involving face and limbs. These movements were accentuated by excitement. She was unable to walk.

Her blood sugar was 560 mg. per cent; urine sugar, 4+; and carbon dioxide combining power, 22.4 mEq. per liter. Blood sugar remained in the 500 to 300 mg. per cent range for thirty days, while the carbon dioxide combining power remained in the 22 to 27 mEq. per liter range. Chemical findings and roentgenograms were unchanged from previous readings.

Without specific treatment, her movements gradually abated and, concurrently, her blood sugar fell. One month later, she had a slight exacerbation of her involuntary movements with a return of hyperglycemia for one or two days. Her movements then virtually disappeared.

Since discharge in January 1957, she has been followed as an outpatient. She remains well with a blood pressure of 225/105, mild left hemiparesis, mild bilateral choreoathetotic movements of her hands, and minimal facial grimaces. Her fasting blood sugar varies between 75 and 90 mg. per cent, and her carbon dioxide combining power is normal.

Case 2. R.D. was a 39-year-old Negro man who died in the Baltimore City Hospitals in 1948. Family, past, and personal histories were noncontributory.

In 1943, a diagnosis of tuberculosis with cavitation in the right upper lobe was made. He was treated with a right pneumothorax and bed rest. He did reasonably well until 1947, when a fresh upper lobe infiltration was discovered. Early in 1948, choreic movements slowly developed in his left leg and foot. During the ensuing month, the movements slowly progressed to the point where they were rapid, writhing, flailing movements of the left foot, leg, arm, and trunk. They were accentuated by anxiety, decreased slightly with rest, and disappeared with sleep.

On neurologic examination, the pupils reacted slowly. Hypotonia of the left arm and leg was found. Power between the movements was bilaterally equal. The reflexes were symmetric initially. Before long, the patient had a mild left hemiparesis, but the movements persisted.

Laboratory studies, including lumbar puncture, were normal.

Six months after onset of movements, the patient was allowed to leave the hospital for the first time in five years. The opinion at that time was that his tuberculosis had healed sufficiently to allow this. His movements were still present at the time of discharge.

Two months after discharge, he was readmitted with one month's history of hemoptysis and coma for four days. His left-sided hyperkinesia continued. His neck was stiff, with a positive kernig's sign. All extremities moved. His reflexes were hypoactive but symmetric.

On his third hospital day, intrathecal streptomycin was added to his intermuscular therapy. This followed the discovery of conjugate deviation of his head and eyes to the left and flaccid right hemiparesis with absent right knee and ankle jerks.

Lumbar puncture disclosed an opening pressure of 160 mm. The fluid contained 300 lymphocytes per cubic millimeter, a protein level of 32 mg. per cent, and a sugar of 30 mg. per cent. Simultaneous blood sugar was 88 mg. per cent. There were numerous bilateral cavities on chest roentgenograms.

He died in coma. Two days before death, right-sided seizures developed. Tuberculous organisms were never cultured from the cerebrospinal fluid or brain.

Postmortem examination showed bilateral pulmonary tuberculosis with tuberculous atelectasis, cavitation, empyema, and caseous lymphadenitis. He had a tuberculous cecum and appendix.

In the nervous system, generalized round cell infiltration was seen. No tuberculous organisms could be stained or cultured. His right subthalamic nucleus was replaced by a tubercle. Figure 1 shows this lesion in the gross. Figure 2 shows the lesion stained for myelin (Weigert). Figure 3 shows the giant cell formation, epithelioid cell infiltration, and an area of necrosis in the lesion (Kinyon).

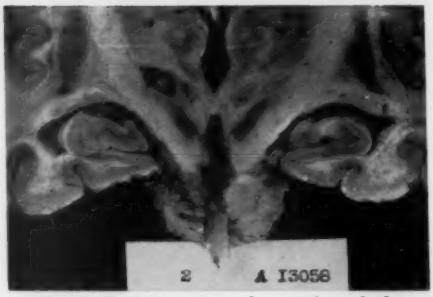

Fig. 1. Posterior aspect of a cut through the corpus luysi

Fig. 2. Right corpus luysi. Weigert stain. × 5

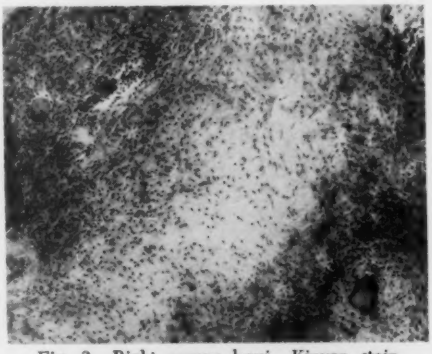

Fig. 3. Right corpus luysi. Kinyon stain. × 150

DISCUSSION

In the first case, the involuntary movements were probably secondary to hypoxia of the corpus luysi, which was a result of her long-standing hypertension and frequent bouts of congestive failure. An additional 14 cases of hemiballismus seen at the Johns Hopkins and Baltimore City hospitals between 1946 and 1959 were reviewed with special attention to the recurrence of symptoms and to sugar metabolism. No patient had recurrent episodes, nor are there reports of any in the literature.

Derangements in sugar metabolism were more common. Of the 15 cases, 4 had preexisting diabetes mellitus. Meyers, in his comments on Hyland and Forman's paper,[15] mentioned a diabetic case of his own, and indeed, almost every series has some. The relationship is, presumably, a reflection of the blood vessel disease in diabetes mellitus and not specifically related to the metabolic upset. There is no evidence of this patient's having an imbalance of sugar regulation before onset of ballism, nor is there any history of diabetes mellitus. In addition to this, she has no evidence of any

difficulty with sugar metabolism after cessation of her acute attacks.

Transient hyperglycemia coincident with bouts of hemiballismus is unique. Gagel[18,19] states that true diabetes mellitus of diencephalic origin is a great rarity but that transient hyperglycemia, with or without glycosuria, is not infrequently seen with disruption in the dynamic interplay of the hypothalamic nuclei. Presumably, the connections to the supraoptic nucleus of the hypothalamus are involved.

The second case is of interest from two standpoints: the slow progression and the discrete tubercle replacing the corpus luysi.

In most other cases, onset of movements is abrupt and, within a very short period (a matter of hours at most), the abnormal activity is at its height. Here, the movements gradually increased in frequency and intensity for thirty days. I would suggest that this was due to the evolution of the tubercle, with more and more destruction of the nuclear mass as the tubercle enlarged.

Wulff's case,[7] which was reviewed by Whittier in 1947,[3] is the only other case of a tubercle in this region. The tubercle was much larger in that instance, involving the internal capsule and substantia nigra as well as the corpus luysi.

SUMMARY

Reports of 2 unique cases of hemiballismus are given. In the first, 3 episodes of transient hemiballismus and hyperglycemia coincided, and, in the second, a discrete tubercle was found in the corpus luysi.

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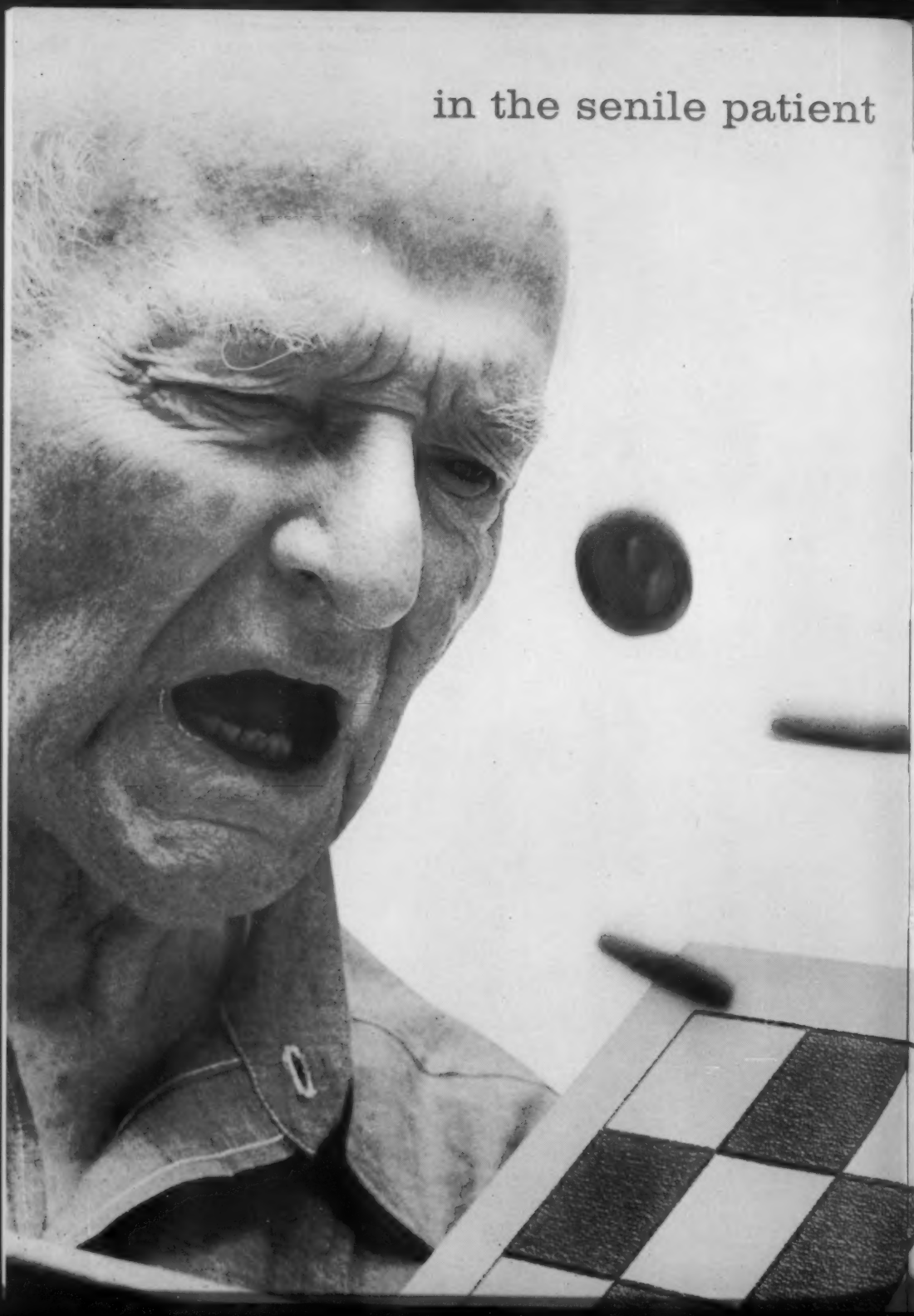

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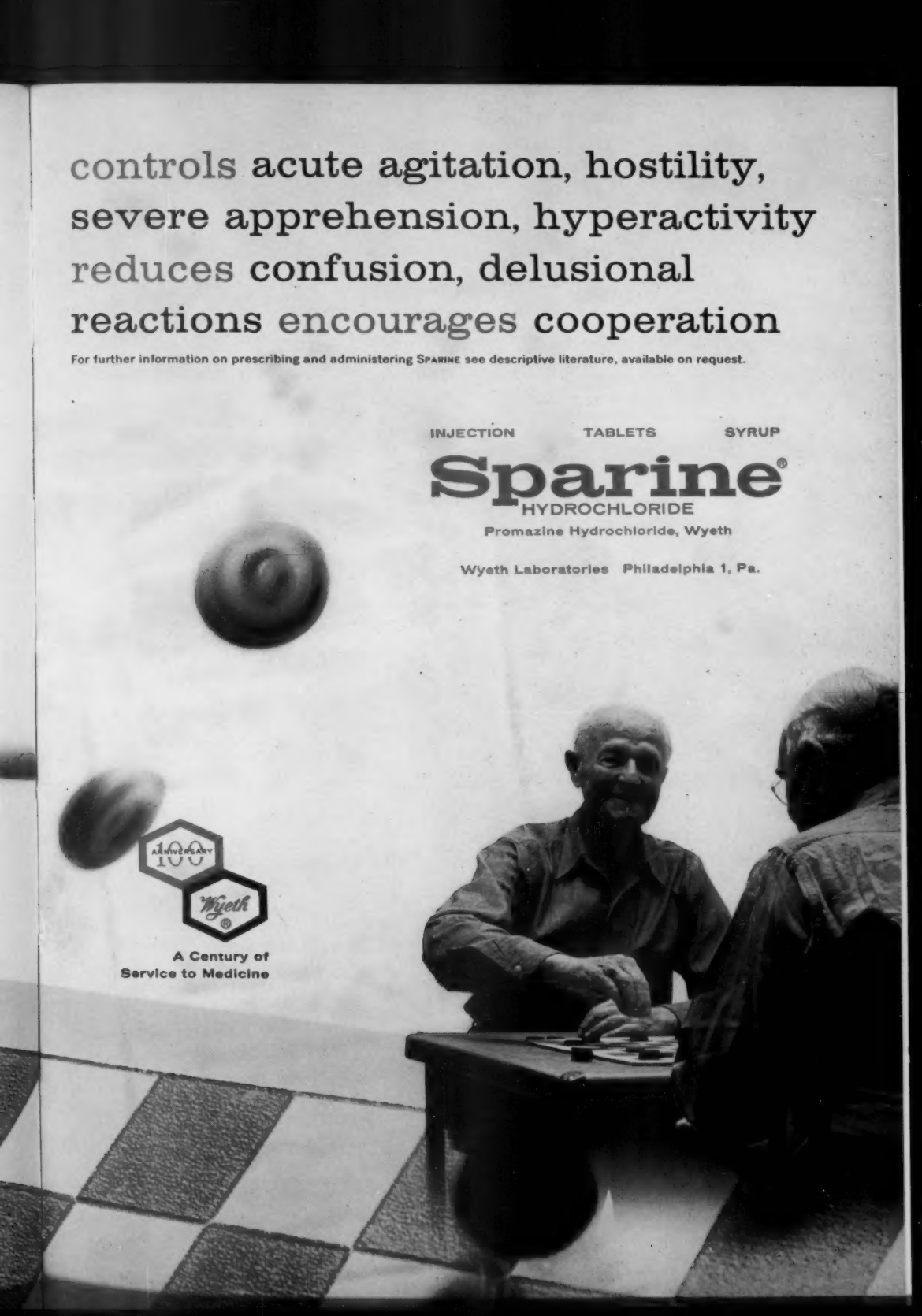

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NEWSLETTER

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JUNE 1960

AAN Holds Annual Meeting at Miami Beach Under the presidency of Augustus S. Rose, the American Academy of Neurology held its twelfth annual meeting at the Eden Roc Hotel in Miami Beach.... The program began with the traditional Special Review Courses (April 25-27) under the Chairmanship of A. B. Baker. The general scientific sessions were held (April 28-30) and also on April 29 there were Section symposia in neuroanatomical sciences, neurochemistry, and neuropharmacology. Presentations from the Child Neurology Section were incorporated within the general scientific sessions (April 29). The Robert Wartenberg Memorial Lecture was given by James W. D. Bull (London) on the "Volume of the Cerebral Ventricles."... Immediately after the close of the regular scientific sessions, an International Conference on Vascular Disease of the Brain, under the Chairmanship of Richard P. Schmidt (Gainesville), was held under Academy auspices and with the sponsorship of the National Institute of Neurological Diseases and Blindness.... Further elaboration of the AAN Miami Beach meeting will appear in the July Newsletter.

Seventh International Congress of Neurology The sessions of the Seventh International Neurological Congress will be held in the auditorium of the Via Della Conciliazione (Palais Pius) in Rome. The official opening will be held at 4:30 P.M., Sunday, September 10 in the Grand Auditorium, followed at 7:30 P.M. by a welcoming reception in the Town Hall (Campidoglio) and in the evening a visit to the "Musés des Capitolins".... The Congress is to be held under the auspices of the World Federation of Neurology and under the sponsorship of the National Institute of Neurological Diseases and Blindness.

Munich and Rome to Feature Neurologic Congresses in 1961 In September 1961, Munich and Rome will be the sites of a series of important international neurologic congresses and symposia. The series will be initiated by the Fourth International Congress of Neuropathology to be held in Munich (September 4-7, 1961). The majority of the other international neurologic meetings will be held in Rome during September 1961. The Fifth International Congress of Electroencephalography will meet September 7-13, 1961, and the Fourth Reunion of the International League Against Epilepsy on the morning of September 10. The Seventh International Neurological Congress, the focal point of the meetings, will be held September 10-15, 1961. The

International Panel on Multiple Sclerosis will hold its meeting on September 15 and the Fourth International Symposium of Neuroradiology will take place September 18-21, 1961..... Current details on these and other international meetings are contained in Information Bulletin Number 2, issued April 15, 1960, by the Secretary-General of the Seventh International Neurological Congress, Prof. Giovanni Alemà, Viale Università, 30, Rome.

Membership Registration and Fees The Congress will have 3 categories of membership: active, open to members of national neurologic societies; associate, open to physicians and scientists having an interest in the Congress; adjunct, open to interested nonprofessionals and to families of members of the Congress. The registration fees are $15 (or equivalent in Italian lire) for active members; $10 for associate members; and $5 for adjunct members. Papers or communications will not be accepted on the program until the proper registration fee has been paid. Registrants may attend free of additional charge all receptions of the Congress, except the official banquet and the evening dance. Attendance at the banquet and the dance is $8 and at the dance only, $3. Registration fees are not redeemable.

Scientific Sessions The scientific program will consist of formal reports and discussions of 3 major topics, communications related to the main topics, and free papers. The latter 2 will be presented according to the digest system adopted at the 1957 Brussels Congress. Each major topic will be considered in its clinical, electroencephalographic, and biochemical aspects. The first major topic deals with neurologic disturbances in porphyrinuria, phenylketonuria, and galactosemia, under the direction of H. Houston Merritt (New York), and will be held as a joint session with the Fifth International Congress of Electroencephalography (Monday, September 11). The second major topic (Tuesday, September 12) concerns neurologic changes in the course of cardiovascular and respiratory disease, under the direction of G. Bodechtel (Munich). This also is a joint session with the International EEG Congress. The third major topic is "Aphasia" with MacDonald Critchley (London) serving as topic director (Thursday, September 14). The digests of communications related to the major topics as well as of free papers will be presented Friday, September 15.

Titles and Abstracts The titles and 500-word abstracts of all communications should be submitted to the President or Secretary of the National Committee of each country in question and thence transmitted to the Secretary-General of the Congress on or before April 15, 1961. If titles and abstracts do not meet this deadline, they will not be printed in the program or in the precirculated brochures. The official languages of the Congress are French, English, German, and Italian....

Related Symposia Important symposia have been planned in conjunction with the Congress and more are in the making. Most symposia will be held on Wednesday, September 13. Among the planned symposia are one in neurochemistry on the "Changes in Myelin," under the direction of A. Lowenthal (Antwerp) and one in geographic neurology, under Leonard A. Kurland (Bethesda). An additional planned symposium on neurogenetics will be held in conjunction with the Third International Conference on Genetics, to be held in Rome (September 7-12)*....Also in the planning under the auspices of the WFN Commission on the History of Neurology is a "travel symposium" on the historical aspects of neurology. According to tentative plans, the participants would hold one-day meetings in Milan, Bologna, and Florence in which the presentation of historical papers and their discussions would be combined with actual visits to the historical sites of these great Italian centers of science and learning. These meetings would take place before the Rome Congress.

Officers of the Congress The President of the Congress is Mario Gozzano and the Secretary-General is Giovanni Alemà, Viale Università 30, Rome....The other members of the Italian National Committee are D. Pisani, V. M. Buscaino, G. B. Belloni, C. Berlucchi, and C. Riquier....More specific details on the Congress will be forthcoming in official Congress information bulletins and in future issues of the NEWSLETTER.

Eleven New Diplomates Certified in Neurology At the Spring Examination of the American Board of Psychiatry and Neurology held in San Francisco (March 14-15, 1960), eleven candidates were certified in neurology. The successful candidates are: E. T. Ajax (Salt Lake City); E. H. Davis (New York); F. A. Horner (Denver); J. Mauceri (New York); J. E. Reinert (Rapid City, S. D.); H. G. Thompson, Jr. (Madison, Wis.); W. W. Tourtellotte (Ann Arbor, Mich.); R. D. Walter (Los Angeles); J. M. Watson (Syracuse, N. Y.); D. D. Webster (Minneapolis); and C. E. Wells (New York).

Korey New President of ARNMD At the annual executive sessions of the Association for Research in Nervous and Mental Disease held at the Hotel Roosevelt, New York City, December 12, 1959, the following officers were elected for 1960: Saul R. Korey, President; Alfred Pope and Eli Robins, Vice Presidents. Rollo J. Masselink continues as Secretary-Treasurer. Dr. S. Bernard Wortis, Chairman of the Board of Trustees to which Lawrence C. Kolb was elected for the term of one year, succeeding the late Edwin G. Zabriskie....The Awards Committee selected Dr. Israel Herbert Sheinberg of the Albert

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*Further information on this symposium may be obtained from its Chairman, Prof. Luigi Gedda, Instituto Mondel, Viale Regina Margaherita, 261, Rome. Other symposia in the making concern the treatment of muscular disease and problems in electromyography....

Einstein College of Medicine as the recipient of the annual $1,000 Award for "his pioneering work on the biochemical defects in heredodegenerative diseases of the nervous system, particularly his elucidation of the role of the deficiency of ceruloplasmin in the causation of hepatolenticular degeneration"....The 1960 meeting of the ARNMD will be held in the Grand Ballroom of New York's Hotel Roosevelt, December 9 and 10, 1960. The subject of the 1960 meeting is "Chemistry: The Nervous System and Behavior."

Montreal Announces International Symposium The University of Montreal is organizing an international symposium on "The Extrapyramidal System and Neuroleptics," to take place at the University of Montreal (November 17-19, 1960). The purpose of the symposium is to provide an exchange of ideas on this subject in its anatomic, physiologic, neurologic, and psychiatric aspects. Expected to participate are 10 Canadian provinces, the United States, and several European countries. Attendance at the symposium is unrestricted but program participation is by invitation only. The official languages are English and French, with simultaneous translations. Further information may be obtained from Dr. Jean-Marc Bordeleau, Department of Psychiatry, University of Montreal, Canada.

Briefs The 85th Annual Meeting of the American Neurological Association will be held at the Statler Hotel, Boston, June 13-15, 1960, under the Presidency of Derek Denny-Brown. Information may be obtained from the Secretary, Melvin D. Yahr, Neurological Institute, 710 West 168th Street, New York 32, N. Y. ....The Third Annual Meeting of the Chilean Society of Neurosurgery will be held July 22 to 24, 1960. The central theme of the meeting is "Neurological and Neurosurgical Sequelae of Birth Trauma." Applications to attend the meeting should be forwarded to the Instituto de Neurocirugia de Chile, Box 70-D, Santiago. President of the Society is Dr. Carlos Villavicencio; the Secretary-General Dr. Juan Fierro M.... The Fifth International Medical Conference to be sponsored by the National Foundation for Infantile Paralysis will be held in London, July 18-22, 1960, on the subject of congenital malformations with some 50 nations expected to participate.... S. Bernard Wortis, well-known Academy Fellow and former President of the American Neurological Association, has been appointed Dean at the New York University School of Medicine and Postgraduate Medical School and Deputy Director of the New York University Medical Center. He succeeds Donal Sheehan who will continue as Professor and Chairman of the Department of Anatomy.

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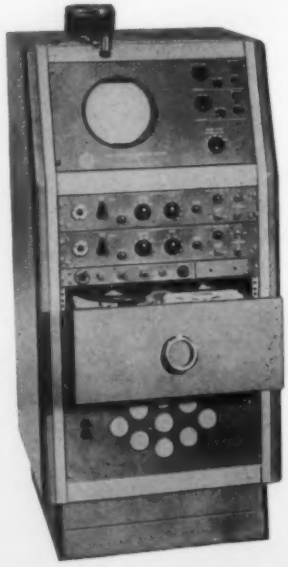

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